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To: Kevin Weddington **Location:** rem/3c70 **Art Unit:** 1614 Friday, October 15, 2004 **Case Serial Number:** 10/064627	**From:** Beverly Shears **Location:** Remsen Bldg. RM 1A54 **Phone:** 571-272-2528 beverly.shears@uspto.gov

Search Notes

Weddington
10/064627


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     FILE 'REGISTRY' ENTERED AT 12:30:12 ON 15 OCT 2004
L1             6 S (NITROGLYCERIN OR ARGININE OR ISOSORBIDE DINITRATE OR SODIUM
                 E "L-ARGININE"/CN 5
L2             1 S E3
L3             6 S L1 OR L2
                 E SILDENAFIL/CN 5
L4             1 S E3

                 E NITROPRUSSIDE/CN 5
L8             2 S E3 OR E5

     FILE 'HCAPLUS' ENTERED AT 12:43:15 ON 15 OCT 2004
L1             6 SEA FILE=REGISTRY ABB=ON  PLU=ON  (NITROGLYCERIN OR ARGININE
                 OR ISOSORBIDE DINITRATE OR SODIUM NITROPRUSSIDE OR PYRIMIDINE)/
                 CN
L2             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  L-ARGININE/CN
L3             6 SEA FILE=REGISTRY ABB=ON  PLU=ON  L1 OR L2
L4             1 SEA FILE=REGISTRY ABB=ON  PLU=ON  SILDENAFIL/CN
L5        149033 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3 OR NITROGLYCERIN OR
                 ANGININE OR NITRODERM OR NITRO(W)(DERM OR BID OR DUR OR STAT)
                 OR NITROBID OR NITRODUR OR GLYCERYL(W)(TRINITRATE OR TRI
                 NITRATE) OR GILUSTENON OR NITROSTAT OR TRINITRIN OR ARGININE
                 OR ARG OR (ISOSORBIDE OR (I OR ISO)(W)SORBIDE)(W)(DINITRATE OR
                 DI NITRATE)
L6         12021 SEA FILE=HCAPLUS ABB=ON  PLU=ON  NITRO(W)(GLYCERIN OR PRUSSIDE
                 OR FERRICYANIDE) OR NITROPRUSSIDE OR NITROFERRICYANIDE OR
                 NANIPRUS OR NIPRUTON OR ISOBID OR ISO BID OR ISODINIT OR
                 DILATRATE OR SORBITRATE OR SORBONIT OR ISORDIL
L7          1134 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 OR SILDENAFIL OR VIAGRA OR
                 (UK 92480 OR UK92480)(W)10
L8             2 SEA FILE=REGISTRY ABB=ON  PLU=ON  NITROPRUSSIDE/CN OR "NITROPRU
                 SSIDE SODIUM"/CN
L9           171 SEA FILE=HCAPLUS ABB=ON  PLU=ON  (L5 OR L6 OR L8 OR PYRIMIDINE)
                  AND L7
L10            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L9 AND ((OCULAR OR OPTIC? OR
                 EYE)(S)(HYPERTENS? OR HYPER TENS? OR (HIGH BLOOD OR HB)(W)PRESS
                 URE OR HBP) OR GLAUCOMA)

L10  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2004 ACS on STN
ED   Entered STN:  15 Nov 2002
ACCESSION NUMBER:         2002:869437  HCAPLUS
DOCUMENT NUMBER:          137:358181
TITLE:                    Nitric oxide donor+cGMP-PDE5 inhibitor as a topical
                          drug for glaucoma
INVENTOR(S):              Shahinpoor, Mohsen; Soltanpour, David; Shahinpoor,
                          Parsa
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 6 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    --------------------    --------
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US 2002168424 A1 20021114 US 2002-64627 20020731
PRIORITY APPLN. INFO.: US 2002-64627 20020731
AB A new topical drug (ointment or **eye** drop) for treating **glaucoma** or **ocular hypertension** in a patient, which comprises a mixture of a nitric oxide donor such as nitrovasodilators like minoxidil, **nitroglycerin**, L-**arginine**, **isosorbide dinitrate**, or **nitroprusside**, and a cyclic guanosine 3',5'-monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5) inhibitor such as **sildenafil** citrate (**Viagra**) in an ophthalmol. acceptable solution mix. In this manner there will be increased blood circulation to the optic nerve and the ocular hypotensive effect of the combined compds. is enhanced synergistically.
IT **55-63-0, Nitroglycerin 74-79-3**, L-**Arginine**, biological studies **87-33-2, Isosorbide dinitrate 14402-89-2**, SOdium **nitroprusside 15078-28-1, Nitroprusside 139755-83-2, Sildenafil**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nitric oxide donor, cGMP, and phosphodiesterase type 5 inhibitors as topical drug for **glaucoma**)

L10 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 15 Feb 2001
ACCESSION NUMBER: 2001:114953 HCAPLUS
DOCUMENT NUMBER: 134:157562
TITLE: Methods and pharmaceutical compositions for increasing optic nerve, choroidal and retinal blood flow by cyclic-GMP analogs, cyclic-GMP phosphodiesterase inhibitors, or guanylate cyclase activators.
INVENTOR(S): Sponsel, William E.
PATENT ASSIGNEE(S): Board of Regents, the University of Texas System, USA
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001010406	A2	20010215	WO 2000-US21929	20000810
WO 2001010406	A3	20020808		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1246605	A2	20021009	EP 2000-952721	20000810
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				

JP 2003506394 T2 20030218 JP 2001-514927 20000810
PRIORITY APPLN. INFO.: US 1999-148150P P 19990810
WO 2000-US21929 W 20000810

AB A method is provided for improving visual function and maximizing the health of the optic nerve and retina by increasing blood flow velocity therein through the application of an effective amount of a formulation of an agent that is a cyclic-GMP analog, a cyclic-GMP phosphodiesterase inhibitor, or a guanylate cyclase activator. Compds. of the invention include e.g. **sildenafil** citrate (**Viagra**).

IT **139755-83-2, Sildenafil**
RL: ADV (Adverse effect, including toxicity); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

IT **55-63-0, Nitroglycerin 15078-28-1, Nitroprusside**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic-GMP analog, cyclic-GMP phosphodiesterase inhibitor, or guanylate cyclase activator for increasing optic nerve, choroidal and retinal blood flow.)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 12:45:05 ON 15 OCT 2004)
L11 11 S L10
L12 11 DUP REM L11 (0 DUPLICATES REMOVED)

L12 ANSWER 1 OF 11 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-388645 [36] WPIDS
CROSS REFERENCE: 1998-348095 [30]; 1999-561067 [47]; 2000-678687 [66]; 2001-158374 [16]; 2001-167741 [17]; 2001-210204 [21]; 2001-272641 [28]; 2001-272642 [28]; 2001-380222 [40]; 2001-388434 [41]; 2001-431621 [46]; 2002-081896 [11]; 2002-224877 [28]; 2002-338324 [37]; 2003-755036 [71]
DOC. NO. CPI: C2004-145469
TITLE: Composition useful for treatment of e.g. sexual dysfunction and hypertension comprises phosphodiesterase inhibitor and endogenous nitric oxide stimulator/endothelium-derived relaxing factor elevator/substrate for nitric oxide synthase.
DERWENT CLASS: B05
INVENTOR(S): EARL, R A; GARVEY, D S; KHANAPURE, S P; TEJADA, I S D
PATENT ASSIGNEE(S): (EARL-I) EARL R A; (GARV-I) GARVEY D S; (KHAN-I) KHANAPURE S P; (TEJA-I) TEJADA I S D
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2004087591	A1	20040506	(200436)*		100

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 2004087591	A1	CIP of	US 1996-740764	19961101
		CIP of	WO 1997-US19870	19971031
		CIP of	US 1998-145142	19980901
		Cont of	US 1999-387727	19990901
		Div ex	US 2001-941691	20010830
		Div ex	US 2002-216866	20020813
			US 2003-694183	20031028

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 2004087591	A1	CIP of	US 5874437
		CIP of	US 5958926
		Cont of	US 6331543
		Div ex	US 6462044

PRIORITY APPLN. INFO: US 1999-387727 19990901; US 1996-740764 19961101; WO 1997-US19870 19971031; US 1998-145142 19980901; US 2001-941691 20010830; US 2002-216866 20020813; US 2003-694183 20031028

AN 2004-388645 [36] WPIDS

CR 1998-348095 [30]; 1999-561067 [47]; 2000-678687 [66]; 2001-158374 [16]; 2001-167741 [17]; 2001-210204 [21]; 2001-272641 [28]; 2001-272642 [28]; 2001-380222 [40]; 2001-388434 [41]; 2001-431621 [46]; 2002-081896 [11]; 2002-224877 [28]; 2002-338324 [37]; 2003-755036 [71]

AB US2004087591 A UPAB: 20040608

NOVELTY - A composition (C1) comprises at least one phosphodiesterase inhibitor (a1), compound (b1) and carrier. (b1) Stimulates endogenous nitric oxide, elevates levels of endogenous endothelium-derived relaxing factor or is a substrate for nitric oxide synthase.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for a kit comprising (a1) and (b1).

ACTIVITY - Endocrine-Gen.; Vasotropic; Hypotensive; Respiratory-Gen.; Cardiovascular-Gen.; Nephrotropic; Cardiant; Antianginal; Antiarteriosclerotic; Antiinflammatory; Hepatotropic; Cerebroprotective; Antiasthmatic; CNS-Gen.; Nootropic; Immunostimulant; Tocolytic; Cytostatic; Uropathic; Antiallergic; Gastrointestinal-Gen.; Ophthalmological. Erectile Responses was evaluated using New Zealand male rabbits (2.6 - 3.0 kg) anesthetized with pentobarbital sodium (30 mg/kg). **Sildenafil** hydrochloride (A) (1 ml) was administered intravenously into the ear vein and S-nitrosoglutathione (B) (200 mu g) was administered by injection intracorporally. Erectile response was measured in terms of intracavernosal blood pressure (ICP). (A), (B) and (A)+(B) showed ICP of 55, 55 and 95 mm Hg respectively. The results showed that the administration of the combination of (A) and (B) gives an unexpected and superior duration that is greater than the additive effect of (A) and (B) individually.

MECHANISM OF ACTION - Phosphodiesterase inhibitor; Endogenous nitric oxide stimulator.

USE - For inducing vasodilation or inhibiting vasospasm of a coronary

artery or bypass graft in mammal (e.g. non-human mammal), for treating a sexual dysfunction in male and female, erectile dysfunction (e.g. vasculogenic impotence) and for treating or preventing a disease induced by the increased metabolism of cyclic guanosine 3',5'-monophosphate e.g. hypertension, pulmonary hypertension, congestive heart failure, renal failure, myocardial infarction, stable, unstable or variant (Prinzmetal) angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, asthma, bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, dementia, immunodeficiency, premature labor, dysmenorrhoea, benign prostatic hyperplasis, bladder outlet obstruction, incontinence, condition of reduced blood vessel patency, postpercutaneous transluminal coronary angioplasty, peripheral vascular disease, allergic rhinitis, **glaucoma** and disease characterized by a gut motility disorder (all claimed) and irritable bowel syndrome.

ADVANTAGE - The composition act synergistically to induce or increase vasodilation or to inhibit vasospasm of coronary artery or bypass graft; and enhances sexual response in males and females.

Dwg.0/60

L12 ANSWER 2 OF 11 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-403334 [38] WPIDS
DOC. NO. CPI: C2003-107506
TITLE: New tetrahydro-(3-chloro-4-methoxybenzylamino)-pyridothienopyrimidine compounds for treating hypertension, myocardial infarct, angina, arteriosclerosis, renal insufficiency, asthma, bronchitis, senility, immunodeficiency, **glaucoma**, etc..
DERWENT CLASS: B02
INVENTOR(S): IKEYAMA, S; SHIINOKI, Y; TAKATA, M; UCHIDA, S; UMEDA, N; YAMADA, H
PATENT ASSIGNEE(S): (NIPS) NIPPON SODA CO
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003035653	A1	20030501	(200338)*	JA	33

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

AU 2002344563	A1	20030506 (200461)	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003035653	A1	WO 2002-JP11028	20021024
AU 2002344563	A1	AU 2002-344563	20021024

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002344563	A1 Based on	WO 2003035653

PRIORITY APPLN. INFO: JP 2001-329605 20011026
AN 2003-403334 [38] WPIDS
AB WO2003035653 A UPAB: 20030616
NOVELTY - 5,6,7,8-Tetrahydro-4-((3-chloro-4-methoxy)benzylamino)-pyrido(4',3':4,5)thieno(2,3-d)**pyrimidine** compounds with a pyridyl or pyrazinyl substituent in the 2 position and an amidino or carbonyl or sulfonyl heterocyclyl substitutent in the 7 position, and their salts, are new.

DETAILED DESCRIPTION - Thienopyrimidine compounds of formula (I) and their salts are new.

A = pyridyl (optionally substituted by OH or halo) or pyrazinyl (optionally substituted by methyl);

B = amidino, di(1-6C)alkylcarbamoyl, di(1-6C)alkylsulfamoyl, or -Y-G;

Y = carbonyl or sulfonyl; and

G = 5-6 membered optionally unsaturated heterocycle containing 1-3 of N, O, S (optionally substituted by halo, OH, 1-4C alkyl, formyl, 1-4C alkylcarbonyl or 1-4C alkoxycarbonyl).

ACTIVITY - Hypotensive; Anti-anginal; Vascular; Nephrotropic; Cardioactive; Heptaotropic; Anti-asthma; Neuroprotectant; Immunostimulant; Sexual disfunction; Cardioprotective.

In tests, 5,6,7,8-tetrahydro-4-((3-chloro-4-methoxy)benzylamino)-2-(4-pyridyl)-7-(3-tetrahydrofuroyl)-pyrido(4',3':4,5)thieno(2,3-d) **pyrimidine** inhibited PDE5 from human platelets with IC50 0.62 nM, compared with 68 nM for PDE6; and this compound decreased the ST change (for anti-angina effect) by -53% compared with -7% for '**Sildenafil** ' and -37% for 5,6,7,8-tetrahydro-4-((3-chloro-4-methoxy)benzylamino)-2-(5-pyrazolyl)-7-methyl-pyrido(4',3':4,5)thieno(2,3-d)**pyrimidine**.

MECHANISM OF ACTION - cGMP-PDE inhibitior.

USE - For treating hypertension, heart failure, myocardial infarct, angina, arteriosclerosis, restenosis after PTCA, pulmonary hypertension, renal insufficiency, renal edema, cardiac edema, hepatic edema, asthma, bronchitis, senility, immunodeficiency, **glaucoma** or impotence.

ADVANTAGE - (I) is selective for PDE5 as against PDE6.

Dwg.0/0

L12 ANSWER 3 OF 11 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-481871 [45] WPIDS
DOC. NO. CPI: C2003-128607
TITLE: Production of cationic non-viral delivery vehicle useful e.g. for DNA lipofection or targeted drug delivery, by conjugating steroid or other drug with polyamine and mixing with lipid.
DERWENT CLASS: A96 B04 B07 D16
INVENTOR(S): DIAMOND, S L; GRUNEICH, J
PATENT ASSIGNEE(S): (UYPE-N) UNIV PENNSYLVANIA
COUNTRY COUNT: 101
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003015757	A1	20030227	(200345)*	EN	70

RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU

MC MW MZ NL OA PT SD SE SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
EP 1424998 A1 20040609 (200438) EN
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
AU 2002324723 A1 20030303 (200452)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003015757	A1	WO 2002-US26152	20020815
EP 1424998	A1	EP 2002-759383	20020815
		WO 2002-US26152	20020815
AU 2002324723	A1	AU 2002-324723	20020815

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1424998	A1 Based on	WO 2003015757
AU 2002324723	A1 Based on	WO 2003015757

PRIORITY APPLN. INFO: US 2002-358138P 20020220; US 2001-312729P 20010816

AN 2003-481871 [45] WPIDS

AB WO2003015757 A UPAB: 20030716

NOVELTY - Production of a cationic non-viral delivery vehicle (A) comprises:

(a) mixing an optionally modified or derivatized steroid (or other drug) (I), a polyamine (II), a conjugating reagent (III) and preferably dimethyl sulfoxide (DMSO), so that (I) is conjugated with (II) by (III);

(b) purifying the (I)-(II) conjugate; and

(c) mixing the conjugate with a lipid (IV).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) (A) prepared as above;

(2) a cationic non-viral delivery vehicle comprising a dexamethasone-spermine molecule and (IV);

(3) methods for facilitating the delivery of compounds to cells or tissues, treating diseases or disorders or facilitating incorporation of compounds into cells, all using (A) (where the mixture in (a) includes DMSO) as delivery vehicle for the compounds, and

(4) kits including (A) (where the mixture in (a) includes DMSO) for administration of (A) or treatment of diseases or disorders.

USE - (A) binds with anionic tissue regions (specifically an anionic domain of a glycosaminoglycan, collagen, fibrin, cellular or erythrocyte glycocalyx, sialic acid, sulfated glycocalyx or isolated nucleic acid), and is useful for delivery of active compounds to tissues (specifically muscle, mucosa, epithelial, nerve, connective, blood, stromal, heart, liver, kidney, skin, brain, intestinal, interstitial space, bone, bone marrow, joint, cartilage, tendon, esophagus, gonad, cerebrospinal fluid,

pancreas, spleen, **ocular**, nasal cavity or hair tissue) or to cells (specifically mammalian cells, especially human endothelial, mesenchymal or neural cells, fibroblasts, neurons, smooth muscle, kidney or liver cells, myoblasts, embryonic, hematopoietic or other stem cells, osteoblasts, chondrocytes, chondroblasts, monocytes, neutrophils, macrophages, retinal nerve cells or epithelial cells), in vivo or in vitro (all claimed). In particular, (A) are used in the treatment of inflammation, asthma, arthritis, pain, joint inflammation, cancer, allergy, **hypertension**, hyperplasia, mestasis, claudication, intimal hyperplasia, hemophilia, coagulopathy, autoimmune disorders, ulcers, erosive esophagitis, heart disorders, pathological hypersecretion, rhinitis, chronic idiopathic urticaria, heartburn, infections, familial adenomatous polyposis, depression, obsessive-compulsive disorder, bulimia nervosa, premenstrual dysphoric disorder, psychosis, schizophrenia, bipolar disorders, generalized or social anxiety disorder, panic, dysmenorrhea, post-traumatic stress, anemia, menopausal symptoms, osteoporosis, hypoestrogenism, kraurosis vulvae, hypercholesterolemia, type II diabetes, Kaposi sarcoma, warts, hepatitis C or B, erectile dysfunction, epilepsy, Paget's disease, neutropenia, progenitor cell mobilization, organ transplant rejection, cluster headache, migraine, angina, **hypertension**, candidiasis, gastritis, cardiac ischemia complications, endometriosis, central precocious puberty, bronchospasm, gastro-esophageal reflux, mastocytosis or proliferative disorders. Typically (A) are used in DNA lipofection.

ADVANTAGE - (A) can be prepared by a one-step method, produce high levels of incorporation in cells or tissues and have good targeting and/or slow release properties.

Dwg.0/6

L12 ANSWER 4 OF 11 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN

ACCESSION NUMBER: 2003-755036 [71] WPIDS

CROSS REFERENCE: 1998-348095 [30]; 1999-561067 [47]; 2000-678687 [66]; 2001-158374 [16]; 2001-167741 [17]; 2001-210204 [21]; 2001-272641 [28]; 2001-272642 [28]; 2001-380222 [40]; 2001-388434 [41]; 2001-431621 [46]; 2002-081896 [11]; 2002-224877 [28]; 2002-338324 [37]; 2004-388645 [36]

DOC. NO. CPI: C2003-207097

TITLE: Composition useful in the treatment of e.g. sexual disorder - comprises a phosphodiesterase inhibitor and a compound that donates nitric oxide or induces production of endogenous nitric oxide or endothelium-derived relaxing factor.

DERWENT CLASS: B02 B05

INVENTOR(S): DE TEJADA, I S; EARL, R A; GARVEY, D S; KHANAPURE, S P

PATENT ASSIGNEE(S): (DTEJ-I) DE TEJADA I S; (EARL-I) EARL R A; (GARV-I) GARVEY D S; (KHAN-I) KHANAPURE S P

COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2003023087	A1	20030130	(200371)*		117

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

US 2003023087	A1	CIP of	US 1996-740764	19961101
		CIP of	WO 1997-US19870	19971031
		CIP of	US 1998-145142	19980901
		Cont of	US 1999-387727	19990901
		Div ex	US 2001-941691	20010830
			US 2002-216886	20020813

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 2003023087	A1	CIP of	US 5874437
		CIP of	US 5958926
		Cont of	US 6331543
		Div ex	US 6462044

PRIORITY APPLN. INFO: US 1999-387727 19990901; US
1996-740764 19961101; WO
1997-US19870 19971031; US
1998-145142 19980901; US
2001-941691 20010830; US
2002-216886 20020813

AN 2003-755036 [71] WPIDS

CR 1998-348095 [30]; 1999-561067 [47]; 2000-678687 [66]; 2001-158374 [16]; 2001-167741 [17]; 2001-210204 [21]; 2001-272641 [28]; 2001-272642 [28]; 2001-380222 [40]; 2001-388434 [41]; 2001-431621 [46]; 2002-081896 [11]; 2002-224877 [28]; 2002-338324 [37]; 2004-388645 [36]

AB US2003023087 A UPAB: 20040608

NOVELTY - A composition (Y1) comprises at least one phosphodiesterase inhibitor and at least one compound (C1) that donates, transfers or releases nitric oxide or endothelium-derived relaxing factor or is a substrate for nitric oxide synthase.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a composition (Y2) comprising the photodiesterase inhibitor and at least one vasoactive agent;

(2) new nitrosated and/or nitrosylated phosphodiesterase inhibitor selected from benzene (substituted on 1-position by R1, 2-position by R2 and 5-position by R3) (I), 5,10-dihydroimidazo(2,1-b)quinazolin-2-one (substituted on 3-position by R8, 6-position by R9, 7-position by R10 and 10-position by R4) (II), 6-methyl-2-oxo-1,2-dihydro-pyridine-3-carbonitrile (substituted on 1-position by R4 and 5-position by R14) (III), 3,7-dihydropurine-2,6-dione (substituted on 1-position by R15, 3-position by R16 and 7-position by R17) (IV), 1H-quinolin-2-one, (substituted on 1-position by R4, 6-position by R18 and 8-position by R8) (V), pyridine (substituted on 4-position by R19) (VI), 8,9-dimethoxy-2-methyl-1,2,3,4,4a,10b-hexahydrobenzo(c) (1,6)naphthyridine (substituted on 6-position by 1,4-phenylene-N(R4)R20) (VII), 4,8-dipiperidin-1-yl-pyrimido(5,4-d)**pyrimidine** (substituted on 2-position by -N(CH2)a-O-D)-(CH2)a-O-D1 and 6-position by -N(-(CH2)a-O-D1)2) (VIII), isoquinoline (substituted on 1-position by -CH2-phenyl (submitted on 3- and 4-position by -O-D2), 6- and 7-position by -O-D2) (IX), R31- (1,3-phenylene (substituted on 4-position by D))-O-R32 (X), compounds of formula (XI)-(XIX); and

(3) a composition (Y3) comprising the nitrosated and/or nitrosylated

phosphodiesterase inhibitor and a carrier.

Full Definitions are given in the DEFINITIONS Field.

ACTIVITY - Vasotropic; Hypotensive; Cardiant; Antianginal; Antiarteriosclerotic; Antiinflammatory; Cerebroprotective; Antiasthmatic; Nootropic; Tocolytic; Gynecological; Analgesic; Cytostatic; Uropathic; Antiallergic; Ophthalmological.

Human corpus cavernosum tissue biopsies were obtained from impotent men. The tissue was placed in Krebs-bicarbonate solution. The tissues were incrementally stretched until optimal tension for contraction was obtained. The tissues were concentrated with phenylephrine (7 x 10-7 M). The tissues were exposed to dipyridamole or 2,6-bis(diethyl(3-methyl-3-(nitrosothiol)butyric acid ester)amino)-4,8-dipiperidinopyrimido-(5,4-d)-**pyrimidine** (A) (10-6 - 3x10-5 M). At the end papaverine (10-4 M) was added to obtain maximal relation. (A) at doses of 10 micro M and 30 micro M was more efficacious in relaxing the phenylephrine-induced contraction that was an equimolar dose of the phosphodiesterase inhibitor dipyridamole.

MECHANISM OF ACTION - Nitrosated and/or Nitrosylated phosphodiesterase inhibitor.

White New Zealand male rabbits (2.6-3) kg were anesthetized with pentobarbital sodium (30 mg/kg). The femoral artery was exposed and indwelled with PE 50 tubing connected to a transducer for recording systemic arterial blood pressure. The ventral part of the penis was then exposed and intracavemosal blood pressure was measured. The contralateral corpus cavernosum was implanted for the administration of drugs. The rabbits were allowed to rest for 10 minutes during which intracavemosal blood pressure (ICP) and mean arterial blood pressure (MABP) were recorded. All drug treatments were administered after stable intracavemosal and systemic blood pressures were established. Animals that did not exhibit an increase in ICP received an injection of a combination of phentolamine (0.2 mg) and papaverine (6 mg). Animals that did not respond to this combination were disregarded from the analysis. **Sildenafil** hydrochloride was prepared as an aqueous solution (injection volume 1 ml) and administered intravenously into the ear vein. S-nitrosoglutathione (SNO-Glu) was prepared as an aqueous solution (200 micro g in 200 micro l) and injection intracorporally. The rabbits were observed after the administration of (i) **sildenafil** hydrochloride alone (ii) the combination of **sildenafil** hydrochloride and SNO-Glu (iii) SNO-Glu alone. The results showed that ICP (% MABP) were 55, 95 and 45 respectively.

USE - For treating a sexual dysfunction in a human patient and for treating or preventing a disease induced by the increased metabolism of cylic guanosine 3',5'-monophosphate such as hypertension, pulmonary hypertension, congestive heart failure, renal failure, myocardial infarction, stable, unstable or variant (Prinzmetal) angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, asthma, bronchitis, chronic obstructive pulmonary disease, cystic fibrosis, dementia, immunodeficiency, premature labor, dysmenorrhoea, benign prostatic hyperplasis, bladder outlet obstruction, incontinence, a condition of reduced blood vessel potency, postpercutaneous transluminal coronary angioplasty, peripheral vascular disease, allergic rhinitis, **glaucoma**, cystic fibrosis, or a disease characterized by a gut motility disorder (all claimed).

ADVANTAGE - The compounds enhances the sexual responses in patients.

Dwg.58/60

L12 ANSWER 5 OF 11 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-338324 [37] WPIDS
CROSS REFERENCE: 1998-348095 [30]; 1999-561067 [47]; 2000-678687 [66]; 2001-158374 [16]; 2001-167741 [17]; 2001-210204 [21]; 2001-272641 [28]; 2001-272642 [28]; 2001-380222 [40]; 2001-388434 [41]; 2001-431621 [46]; 2002-081896 [11]; 2002-224877 [28]; 2003-755036 [71]; 2004-388645 [36]
DOC. NO. CPI: C2002-097220
TITLE: New nitrosated and/or nitrosylated phosphodiesterase inhibitor useful in the treatment of e.g. sexual disorders, hypertension, renal failure, stroke or gut mobility disorders.
DERWENT CLASS: B05
INVENTOR(S): EARL, R A; GARVEY, D S; KHANAPURE, S P; TEJADA, I S D; SAENZ DE TEJADA, I
PATENT ASSIGNEE(S): (EARL-I) EARL R A; (GARV-I) GARVEY D S; (KHAN-I) KHANAPURE S P; (TEJA-I) TEJADA I S D; (NITR-N) NITROMED INC
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002019405	A1	20020214	(200237)*		110
US 6462044	B2	20021008	(200274)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 2002019405	A1	CIP of	US 1996-740764	19961101
		CIP of	WO 1997-US19870	19971031
		CIP of	US 1998-145142	19980901
		Cont of	US 1999-387727	19990901
			US 2001-941691	20010830
US 6462044	B2	CIP of	US 1996-740764	19961101
		CIP of	WO 1997-US19870	19971031
		CIP of	US 1998-145142	19980901
		Cont of	US 1999-387727	19990901
			US 2001-941691	20010830

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 2002019405	A1	CIP of	US 5874437
		CIP of	US 5958926
US 6462044	B2	CIP of	US 5874437
		CIP of	US 5958926
		Cont of	US 6331543

PRIORITY APPLN. INFO: US 1999-387727 19990901; US 1996-740764 19961101; WO 1997-US19870 19971031; US 1998-145142 19980901; US 2001-941691 20010830

Searcher : Shears 571-272-2528

AN 2002-338324 [37] WPIDS
CR 1998-348095 [30]; 1999-561067 [47]; 2000-678687 [66]; 2001-158374 [16]; 2001-167741 [17]; 2001-210204 [21]; 2001-272641 [28]; 2001-272642 [28]; 2001-380222 [40]; 2001-388434 [41]; 2001-431621 [46]; 2002-081896 [11]; 2002-224877 [28]; 2003-755036 [71]; 2004-388645 [36]
AB US2002019405 A UPAB: 20040608
NOVELTY - Nitrosated and/or nitrosylated phosphodiesterase inhibitors are new.

DETAILED DESCRIPTION - Nitrosated and/or nitrosylated phosphodiesterase inhibitor comprises compound(s) of formula (I)-(XIX).

R1 = alkoxy, (cyclo)alkoxy, halogen or (substituted) 1-methyl-3-propyl-1,6-dihydro-pyrazolo(4,3-d)pyrimidin-7-one-5-yl;

R2 = H, or (halo)alkoxy;

R3 = -Z1, etc.;

P1 = 3,4-dihydro-1H-quinolin-2-one-6-yl (substituted on 1-position by R4);

P2 = piperazine-1,4-diyl;

P3 = 3,4-dihydroquinoline-2,6-diyl;

P4 = (substituted) imidazolidin-2-one-5-yl;

Z1 = (substituted) pyrrolidin-2-one-4-yl;

Z2 = (substituted) 1,3,thiazinan-4-one;

Z3 = (substituted) pyridazine;

Z4 = -N(R4)-C(O)-or -N=C(S-R4)-;

Z5 = (substituted) thiazole;

D = -NO, NO2, etc.;

Rd = H, lower alkyl, cycloalkyl, aryl or arylalkyl;

Re, Rf = H, alkyl, cycloalkoxy, halogen, hydroxy, etc.;

Re+Rf = carbonyl, etc.;

p' = carbonyl, phosphoryl or silyl;

l, t = 1-3;

r, s, c, d, g, i and j = 0-3;

w, x, y and z = 0 - 10;

P1 = covalent bond or P';

B = alkyl, aryl or (C(Re)(Rf))p;

E = -T-, alkyl, aryl or -(CH2CH2O)q;

q = 1 - 5;

L = -C(O)-, C(S)-, -T-, etc.;

W = O, S(O)n' or NRi;

n' = 0 - 2;

Ri = H, alkyl, aryl, alkylcarboxylic acid, etc.;

M+ = (in)organic cation;

F' = B or carbonyl;

n = 2 - 5;

R4 = H, -CH(Rd)-O-C(O)-Y-Z-(C(Re)(Rf))p-TQ, -C(O)-T-(C(Re)(Rf))p-T-Q, etc.;

R5 = a lone pair of electrons or -CH(Rd)-O-C(O)-Y-Z-(C(Re)(Rf))p-T-Q;

R11 = H or R4;

X = halo;

D1 = D or H;

R8 = H, lower alkyl or haloalkyl;

R9 = H or halo;

R10 = H, -C(Z6)=N-O-CH2-C(O)-N(R8)Z7 etc.;

Z6 = phenyl;

Z7 = cyclohexyl;

E1 = N or -CH-;

G1 = N or -C(R8)-;

R22 = R12 or lower alkyl;
R33 = lower alkyl or (C(Re)(Rf))p-T-Q;
G2 = -CH2 or S;
R13 = 4-(1H-imidazolyl)-thiophene-2-yl, etc.;
R6, R7 = R4;
R14 = quinolin-6-yl, etc.;
R15 = H, lower alkyl, etc.;
R16 = lower alkyl;
R17 = H, lower alkyl, etc.;
R18 = 2,4-dimethyl pyrrole-1-yl, etc.;
Z8 = R4 or R12;
Z9 = NC or R11N;
R20 = -C(O)-CH3, etc.;
Z10 = 1,4-phenylene;
a = 2 - 3;
D2 = H, lower alkyl or D;
Y = O, S(O)n', lower alkyl or NRi;
p = 1-10;
G = bond, -T-C(O)-, etc.;
b = 0-5;
J = -Z11, etc.;
Z11 = (substituted) phenyl;
R24 = K'-G-D or H;
K' = 1,4-cyclohexyl, 1,4-piperidinyl or -Y-(CH2)P-;
A1, A2 or A3 = subunit of monocyclic aromatic, etc.;
R23 = D, H, halo, etc.;
Ba, Bb = N or C-R23;
R26-R30 = H, halo, etc.;
R31 = alkyl, halo, haloalkyl or haloalkoxy;
R32 = D or -C(O)-R8;
A = CH2, carbonyl or methanethial;
G4 = O or S;
R34 = H, lower alkyl, etc.;
R35 and R36 = H, lower alkyl, etc.;
R35+R36 = carbonyl, methanethial, etc.;
R34+R35 = (C(Rg)(Rh))u etc.;
u = 3 or 4;
v = 1 or 2
T = covalent bond, O, S(O)n, or NRi;
Rg, Rh = H, alkyl, T-Q, etc.;
R38 = H, halogen or lower alkyl;
R37 = -Z11, etc.;
R25 = H, alkyl, cycloxy, etc.;
R40 = H, lower alkyl, etc.;
R41 = lower alkyl, hydroxyalkyl, etc.;
R42 = -M2, -CH2-M2 or -(CH2)a-O-CH2-M2;
M2 = (substituted) phenyl;
R44 = -Z11, (substituted) pyridinyl, etc.;
R46, R47 = lower alkyl, hydroxyalkyl or D; and
NR46+R47 = heterocyclic ring.

INDEPENDENT CLAIMS are also included for:

(1) composition (A1) containing at least one of (I)-(XIX) and a carrier or at least one compound (C1) that denotes transfer or release nitric oxide, includes the production of endogenous nitric oxide, endothermic derived relaxing factor or is a substrate for nitric oxide synthase;

(2) composition (A2) comprising phosphodiesterase inhibitor(s) and (C1); and

(3) composition (A3) comprising phosphodiesterase inhibitor(s) and vasoactive agent(s).

ACTIVITY - Vasotropic; Hypotensive; Cardiant; Antiangial; Antiarteriosclerotic; Antiinflammatory; Cerebroprotective; Antiasthmatic; Nootropic; Tocolytic; Gynecological; Analgesic; Cytostatic; Uropathic; Antiallergic; Ophthalmological.

Human corpus cavernosum tissue biopsies were obtained from impotent men. The tissue was placed in Krebs-bicarbonate solution and incrementally stretched until optimal tension for contraction was obtained. The tissues were concentrated with phenylephrine (7 multiply 10-7 M) and exposed to dipyridamole or 2,6-bis(diethyl(3-methyl-3(nitrosothiol)butyric acid ester)amino)-4,8-dipiperidinopyrimido-(5,4-d)-pyrimidine (A) (10-6-3 multiply 10-5 M). At the end papaverine (10-4 M) was added to obtain maximal relaxation.

(A) at doses of 10 mu M and 30 mu M was more efficacious in relaxing the phenylephrine-induced contraction that was an equimolar dose of the phosphodiesterase inhibitor dipyridamole.

MECHANISM OF ACTION - Nitrosated and/or Nitorsylated phosphodiesterase inhibitor.

White New Zealand male rabbits (2.6-3) kg were anesthetized with pentobarbital sodium (30 mg/kg). The femoral artery was exposed and indwelled with a PE 50 tubing connected to a transducer for recording systemic arterial blood pressure. Ventral part of penis was exposed and intracavernosal blood pressure was measured. Contralateral corpus cavernosum was implanted for administration of drugs.

Rabbits were allowed to rest for 10 minutes during which intracavernosal blood pressure (ICP) and mean arterial blood pressure (MABP) were recorded. All drug treatments were administered after stable intracavernosal and systemic blood pressures were established.

Animals that did not exhibit increase in ICP received injection of phenolamine (0.2 mg) and papaverine (6 mg). Animals that did not respond to this combination were disregarded from analysis. Sildenafil hydrochloride was prepared as aqueous solution (injection volume 1 ml) and administered intravenously into ear vein. S-nitrosoglutathione (SNO-Glu) was prepared as aqueous solution (200 mu g in 200 mu l) and injected intracorporally.

Rabbits were observed after administration of (i) sildenafil hydrochloride alone (ii) combination of sildenafil hydrochloride and SNO-Glu (iii) SNO-Glu alone. Results showed that ICP (% MABP) were 55, 95 and 45 respectively.

USE - To treat sexual dysfunction and to treat or prevent disease induced by increased metabolism of cyclic guanosine 3',5'-monophosphate e.g. hypertension, pulmonary hypertension, congestive heart failure, renal failure, myocardial infarction, stable, unstable or variant (Prinzmetal) angina, atherosclerosis, cardiac edema, renal insufficiency, nephrotic edema, hepatic edema, stroke, asthma, bronchitis, chronic obstructive pulmonary disease, dementia, immunodeficiency, premature labor, dysmenorrhoea, benign prostatic hyperplasis, bladder outlet obstruction, incontinence, condition of reduced blood vessel potency, postpercutaneous transluminal coronary angioplasty, peripheral vascular disease, allergic rhinitis, glaucoma, cystic fibrosis, or disease characterized by gut motility disorder (all claimed).

ADVANTAGE - Compounds enhance sexual responses in patients.

Dwg.0/60

L12 ANSWER 6 OF 11 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-611254 [70] WPIDS
DOC. NO. CPI: C2001-182553
TITLE: Treatment of erectile dysfunction without inducing circulatory side-effects, using penis-specific phosphodiesterase V inhibitors, preferably benzo (4,5) thieno (2,3-d) **pyrimidine** derivatives.
DERWENT CLASS: B02
INVENTOR(S): BRAENDLE, M; EHRING, T; WILM, C; BRANDLE, M
PATENT ASSIGNEE(S): (MERE) MERCK PATENT GMBH; (BRAN-I) BRANDLE M; (EHRI-I) EHRING T; (WILM-I) WILM C
COUNTRY COUNT: 92
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001064192	A2	20010907	(200170)*	GE	32
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
DE 10010612	A1	20010927	(200170)		
AU 2001037379	A	20010912	(200204)		
EP 1259229	A2	20021127	(200302)	GE	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
US 2003022906	A1	20030130	(200311)		
JP 2004504269	W	20040212	(200413)		58
MX 2002008571	A1	20030201	(200413)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001064192	A2	WO 2001-EP1557	20010213
DE 10010612	A1	DE 2000-10010612	20000303
AU 2001037379	A	AU 2001-37379	20010213
EP 1259229	A2	EP 2001-909743	20010213
		WO 2001-EP1557	20010213
US 2003022906	A1	WO 2001-EP1557	20010213
		US 2002-220416	20020903
JP 2004504269	W	JP 2001-563089	20010213
		WO 2001-EP1557	20010213
MX 2002008571	A1	WO 2001-EP1557	20010213
		MX 2002-8571	20020902

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001037379	A	Based on	WO 2001064192
EP 1259229	A2	Based on	WO 2001064192
JP 2004504269	W	Based on	WO 2001064192

Searcher : Shears 571-272-2528

MX 2002008571 A1 Based on WO 2001064192

PRIORITY APPLN. INFO: DE 2000-10010612 20000303
AN 2001-611254 [70] WPIDS
AB WO 200164192 A UPAB: 20011129
NOVELTY - The use of highly penis-specific phosphodiesterase V (PDE V) inhibitors (I) (including their salts and/or solvates) is claimed in the preparation of medicaments for treating erectile dysfunction without inducing the circulatory side-effects usually caused by PDE V inhibitors.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:

(i) pharmaceutical compositions comprising (I); and

(ii) benzo (4,5) thieno (2,3-d) **pyrimidine** derivatives of formula (I') (including their salts and/or solvates) as highly penis-specific PDE V inhibitors.

R1, R2 = H, A, OA, OH or halo; or

R1 + R2 = 3-5C alkylene, OCH2CH2, CH2OCH2, OCH2O or OCH2CH2O;

X = R4, R5 or R6, all monosubstituted by R7;

R4 = 1-10C alkylene (in which 1 or 2 CH2 groups may be replaced by CH=CH);

R5 = cycloalkyl or cycloalkylalkylene having 5-12C;

R6 = phenyl or phenylmethyl;

R7 = COOH, COOA, CONH2, CONHA, CON(A)2 or CN; and

A = 1-6C alkyl.

ACTIVITY - Vasotropic; antianginal; hypotensive; antiarteriosclerotic; cerebroprotective; antiinflammatory; antiasthmatic; antiallergic; ophthalmological; cytostatic; nephrotropic; hepatotropic.

In tests in anesthetized dogs, 4-(4-(3-chloro-4-methoxy-benzylamino)-benzo (4,5) thieno (2,3-d) pyrimidin-2-yl)-cyclohexane carboxylic acid ethanolamine salt (I'a) at 1 mg/kg i.d. potentiated sub-maximal erection without any effects on hemodynamic parameters, whereas **sildenafil** even at this dosage affected blood pressure and cardiac frequency.

MECHANISM OF ACTION - Penis-specific PDE V inhibitor.

USE - (I), especially the preferred compounds (I'), are useful for treating erectile dysfunction without inducing the circulatory side-effects caused by conventional PDE V inhibitors, especially when used simultaneously with vasodilators acting on via the nitrogen monoxide-cyclic guanosine monophosphate (NO-cGMP) system (specifically nitrates) (all claimed). (I) may also be useful for treating sexual disorders in females without causing circulatory side-effects; and (I') may additionally be useful in the treatment of angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, reduced cardiovascular blood flow, perpheral vascular disease, stroke, bronchitis, allergic or chronic asthma, allergic rhinitis, **glaucoma**, irritable bowel syndrome, tumors, renal insufficiency or liver cirrhosis (not claimed).

ADVANTAGE - (I) have selective action on the penis, due to inhibition of a penis-specific subtype of PDE V and/or as a result of selective transport to the penis effector cells and rapid elimination from the effector cells of the cardiovascular system. (I) thus do not cause the cardiovascular side-effects (e.g. hypotension and rebound increase in heart frequency) often occurring on administration of **Viagra** (RTM; **sildenafil**) and other conventional PDE V inhibitors, especially when used in combination with nitrate compounds such as **nitroglycerin**.

Dwg.0/0

L12 ANSWER 7 OF 11 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-138727 [14] WPIDS
DOC. NO. CPI: C2001-041066
TITLE: Methods of increasing optic nerve, choroidal and retinal blood flow to facilitate the preservation of sight.
DERWENT CLASS: B05
INVENTOR(S): SPONSEL, W E
PATENT ASSIGNEE(S): (TEXA) UNIV TEXAS SYSTEM
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001010406	A2	20010215	(200114)*	EN	54
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000065365	A	20010305	(200130)		
EP 1246605	A2	20021009	(200267)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
JP 2003506394	W	20030218	(200315)		61

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001010406	A2	WO 2000-US21929	20000810
AU 2000065365	A	AU 2000-65365	20000810
EP 1246605	A2	EP 2000-952721	20000810
		WO 2000-US21929	20000810
JP 2003506394	W	WO 2000-US21929	20000810
		JP 2001-514927	20000810

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000065365	A	Based on	WO 2001010406
EP 1246605	A2	Based on	WO 2001010406
JP 2003506394	W	Based on	WO 2001010406

PRIORITY APPLN. INFO: US 1999-148150P 19990810
AN 2001-138727 [14] WPIDS
AB WO 200110406 A UPAB: 20011129
NOVELTY - Method for improving visual function and optimizing the health of the optic nerve and retina by increasing blood flow by a composition including an agent that increases cyclic-guanosine monophosphate (cyclic-GMP) levels, either directly, or by stimulating cyclic-GMP synthesis or by inhibiting cyclic-GM selective phosphodiesterase(s).
DETAILED DESCRIPTION - A method for treating an optic nerve disease comprises administering a composition comprising at least a first agent that increases ocular blood flow by elevating levels of cyclic-GMP.

Searcher : Shears 571-272-2528

INDEPENDENT CLAIMS are also included for the following:
(1) a method of treating retinal disease using above composition;
(2) a method of treating choroidal disease using above composition;
(3) a method for increasing ocular blood flow comprising administering a composition comprising at least a first cyclic-GMP phosphodiesterase inhibitor to a patient suffering from a macular disorder;
(4) a method for treating macular edema, comprising administering a composition containing at least a first agent that increases cyclic-GMP;
(5) a method for inhibiting or preventing the accumulation of lipofuscin in an eye comprising administering a composition comprising at least a first agent that inhibits phosphodiesterase type 5;
(6) a method for increasing ocular blood flow comprising administering a composition comprising at least a first agent that activates guanylate cyclase;
(7) a method for increasing ocular blood flow comprising administering a composition comprising at least a first agent that increases ocular nitric oxide levels;
(8) a kit for treatment of ocular disorders comprising:
(i) a sealed container housing a composition comprising at least a first agent that increases ocular blood flow by elevating levels of cyclic-GMP; and
(ii) instructions for administering composition;
(9) a composition for increasing ocular blood flow, comprising at least a first compound that increases ocular levels of cyclic-GMP;
(10) a method for treating optical nerve disease comprising administering **sildenafil** citrate;
(11) a method for treating choroidal disease comprising administering **sildenafil** citrate;
(12) a method for increasing visual function comprising administering **sildenafil** citrate to an affected eye;
(13) a method for increasing ocular blood flow comprising administering **sildenafil** citrate;
(14) a method for increasing visual function comprising administering to a patient with normal vision **sildenafil** citrate; and
(15) an ophthalmic preparation comprising a carrier and **sildenafil** citrate at a concentration of 0.001 - 20 % weight per volume.

ACTIVITY - Ophthalmological.

MECHANISM OF ACTION - Cyclic-GMP phosphodiesterase inhibitor; guanylate cyclase activator

USE - For the treatment of **optical** nerve disease from normotensive excavatory **optic** neuropathy, ischemic **optic** neuropathy, toxic **optic** neuropathy, traumatic **optical** neuropathy or idiopathic **optic** neuropathy. The idiopathic **optic** neuropathy may be **optic** nerve drusen or benign intracranial **hypertension**. For the treatment of retinal disease including retinal neovascularization, ischemic hematologic/rheologic disorders or toxic maculpathy. For treating choroidal disease, especially when it is an ischemic disorder of the posterior choroid, degenerative subretinal neovascularization, diabetic choroidal ischemia, inflammatory subretinal neovascularization or non-age related choroidal ischemia. The ischemic disorder of the posterior choroid may be degenerative drusen of the macula, macular retinal pigment epithelial atrophy, or retinal pigment epithelial detachment. The degenerative subretinal neovascularization may be wet age related mascular degeneration. Useful for the treatment of

mascular disorders including macular edema, macular degeneration, familial drusen, macular disorders due to **hypertension**, angioma, papillitis, neuroretinitis or pigmentary retinal degenerative disorders. The macular edema is with vascular leakage from diabetic retinopathy, branch retinal vein occlusion, intermediate uveitis or ideopathic retinal telangiectasis.

May also be used for increasing visual function comprising administering **sildenafil** citrate to an affected eye, and may be used for increasing visual function for a patient with normal vision. Dwg.0/11

L12 ANSWER 8 OF 11 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001348399 EMBASE
TITLE: Role of nitric oxide in the control of ocular blood flow.
AUTHOR: Schmetterer L.; Polak K.
CORPORATE SOURCE: L. Schmetterer, Department of Clinical Pharmacology, Vienna General Hospital, University of Vienna, Wahringer Gurtel 18-20, A-1090 Vienna, Austria. leopold.schmetterer@univie.ac.at
SOURCE: Progress in Retinal and Eye Research, (2001) 20/6 (823-847). Refs: 251 ISSN: 1350-9462 CODEN: PRTRES
PUBLISHER IDENT.: S 1350-9462(01)00014-3
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
012 Ophthalmology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB In the recent years it has been recognized that nitric oxide is an important regulator of ocular blood flow. Nitric oxide is involved in the control of basal blood flow in the choroid, optic nerve and the retina. In addition, nitric oxide mediates a number of vasodilator responses in ocular vessels to agonists such as acetylcholine, bradykinin, histamine, substance P and insulin. Nitric oxide also plays a role in hypercapnia-induced vasodilation in the choroid and is a modulator of pressure autoregulation in this vascular bed. Abnormalities of the L-**arginine**/nitric oxide system have been observed in a variety of ocular diseases including **glaucoma**, diabetic retinopathy and retinopathy of prematurity. This makes the L-**arginine**/nitric oxide pathway an attractive target for therapeutic interventions. Additional research is required, particularly in characterizing the role of the three nitric oxide synthase isoforms in the control of ocular perfusion, to implement this concept into the clinical management of ocular diseases. .COPYRGT. 2001 Elsevier Science Ltd. All rights reserved.

L12 ANSWER 9 OF 11 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-638460 [61] WPIDS
DOC. NO. CPI: C2000-192092
TITLE: New thieno(2,3-d)**pyrimidine** compounds are specific cGMP phosphodiesterase inhibitors useful as vasodilators for treating e.g. hypertension, renal insufficiency, asthma and dementia.

DERWENT CLASS: B02
INVENTOR(S): HORIKOSHI, H; MOCHIZUKI, N; SHIINOKI, Y; UCHIDA, S; UMEDA, N; YAMADA, H
PATENT ASSIGNEE(S): (NIPS) NIPPON SODA CO
COUNTRY COUNT: 91
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000059912	A1	20001012	(200061)*	JA	51
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000034539	A	20001023	(200107)		
EP 1167367	A1	20020102	(200209)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
KR 2001105399	A	20011128	(200233)		
CN 1346358	A	20020424	(200251)		
JP 2000609423	X	20020716	(200261)		
US 6482948	B1	20021119	(200280)		
EP 1323719	A1	20030702	(200344)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000059912	A1	WO 2000-JP1957	20000329
AU 2000034539	A	AU 2000-34539	20000329
EP 1167367	A1	EP 2000-912919	20000329
		WO 2000-JP1957	20000329
KR 2001105399	A	KR 2001-712337	20010927
CN 1346358	A	CN 2000-805982	20000329
JP 2000609423	X	JP 2000-609423	20000329
		WO 2000-JP1957	20000329
US 6482948	B1	WO 2000-JP1957	20000329
		US 2001-914825	20010831
EP 1323719	A1 Div ex	EP 2000-912919	20000329
		EP 2003-4562	20000329

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000034539	A	Based on	WO 2000059912
EP 1167367	A1	Based on	WO 2000059912
JP 2000609423	X	Based on	WO 2000059912
US 6482948	B1	Based on	WO 2000059912
EP 1323719	A1	Div ex	EP 1167367

PRIORITY APPLN. INFO: JP 1999-102287 19990409; JP 1999-87547 19990330

Searcher : Shears 571-272-2528

AN 2000-638460 [61] WPIDS
AB WO 200059912 A UPAB: 20001130
NOVELTY - Thieno(2,3-d)**pyrimidine** compounds (I) are new.
DETAILED DESCRIPTION - Thieno(2,3-d)**pyrimidine** compounds of formula (I) and their salts are new.
Q = (CH2)nNr1Cr2r3, CH=CHCH=CH or (CH2)m;
r1 = H, Alk, SO2Alk, CH2Ph, COr4 or COOr5;
Ph = phenyl (optionally substituted by G1);
r2, r3 = H, Alk, or Ph; or
r2 + r3 = O;
r4 = H, Alk, 2-6C alkenyl, Ph, or Het;
Het = optionally unsaturated heterocyclyl containing 1-4 N, O or S and optionally substituted by G3;
r5 = H, Alk, 2-6C alkenyl or Ph;
n = 1-3;
m = 3-5;
R1 = H or Alk;
R2 = 3-8C cycloalkyl (optionally substituted by G1), Ph1 or Het;
Ph1 = phenyl (optionally substituted by G2);
R3 = Het, (CH2)kCOR4 or CH=CHCOR4;
R4 = OH, 1-6C alkoxy, OPh1, OCH2Ph1, Nr6r7 or NHNr8r9;
r6, r8 = H or Alk;
r7, r9 = H, 3-8C cycloalkyl, COAlk, Alk AlkHet, Ph, CH2Ph or Het; or
r6+r7 = CH2CH2Y'CH2CH2;
Y' = O, CH2 or Nr10;
r10 = H, Alk, Ph or CH2Ph;
k = 0-2;
G1 = halo, Alk or OAlk;
G2 = halo, Alk, OAlk or 1 or 2C alkylenedioxy;
G2 = halo, Alk OAlk or COOAlk;
Alk = 1-6C alkyl;
provided that when R3 = Het then Q is not (CH2)nNr1Cr2r3; and when Q = (CH2)m or CH=CHCH=CH and R4 = anilino then k is not 0.
ACTIVITY - Vasotropic; hypotensive; cardiant; antianginal; antiarteriosclerotic; nephrotropic; antiasthmatic; antiinflammatory; nootropic; immunomodulator; ophthalmolgical; neuroprotective. In a vasodilation test on isolated Sprague-Dawley rat aorta 5,6,7,8-tetrahydro-4-((3-chloro-4-methoxy)benzylamino)-7-ethoxycarbonyl-2-(3-pyridyl)pyrido(4',3':4,5)thieno(2,3-d)**pyrimidine** (Ia) had an EC50 of 2.1 nM compared to 6.1 nM for **sildenafil**.
MECHANISM OF ACTION - Phosphodiesterase V inhibitor.
USE - (I) are useful as cGMP phosphodiesterase inhibitors useful as vasodilators and for treating and preventing hypertension, cardiac insufficiency, myocardial infarction, angina, arteriosclerosis, reocclusion after percutaneous transluminal angioplasty, myocardial edema, pulmonary hypertension, renal insufficiency, renal edema, pulmonary edema, asthma, bronchitis, dementia, immune diseases, glaucoma and sexual impotence.
ADVANTAGE - (I) are highly specific for cGMP phosphodiesterase and thus have reduced side effects.
Dwg.0/0

L12 ANSWER 10 OF 11 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-572170 [53] WPIDS
DOC. NO. CPI: C2000-170623
TITLE: New nitrosated and nitrosylated prostaglandins, useful

for treating or preventing e.g. sexual dysfunction in males and females, cerebrovascular disorders and **glaucoma.**

DERWENT CLASS: B05
INVENTOR(S): GARVEY, D S; GASTON, R D; LETTS, G L; SAENZ DE TEJADA, I; TAM, S W; WORCEL, M
PATENT ASSIGNEE(S): (NITR-N) NITROMED INC
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000051978	A1	20000908	(200053)*	EN	82

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000037136	A	20000921	(200065)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000051978	A1	WO 2000-US5286	20000301
AU 2000037136	A	AU 2000-37136	20000301

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000037136	A	Based on	WO 2000051978

PRIORITY APPLN. INFO: US 1999-138502P 19990609; US 1999-122273P 19990301

AN 2000-572170 [53] WPIDS
AB WO 200051978 A UPAB: 20001023
NOVELTY - Nitrosated and nitrosylated prostaglandins (I) and compositions comprising them are new, also compositions comprising a prostaglandin and S-nitrosothiol compound.

DETAILED DESCRIPTION - Nitrosated and nitrosylated prostaglandins of formula (I) are new:

bonds a', b', c', d' = single or double bonds;
R1 = -OD1 or Cl;
R2, R8 = H; or
R1+R2 = =CH2 or =O;
R3, R4 = H, -OD1 or Me;
R5, R6 = H, -OD1, Me, OMe or -CH=CH2;
R7 = H or OD1;
R9 = H or absent when the C to which it is attached is the central carbon of an allene; or
R8+R9+attached chain atoms = a substituted benzene ring provided that R1 is O which is attached to the C at the position of the benzene ring defined by B';
A = -CH=, -CH2-, -S- or -O-;

B' = -CH=, -CH2-, -S- or -C(O)-;
X = -CH2OR11, -C(O)OR11 or -C(O)N(D1)R12;
R11 = D1, 1-10C alkyl or a group of formula (i):
R12 = -S(O)2CH3 or -C(O)CH3;
Z' = ethyl, butyl, hexyl, benzyl, -CH2-O-CH2-CH3, -CH(CH3)-(CH2)3-CH3 or a group of formula (ii) or (iii):
R13 = H or Cl;
D1 = H or D; provided that at least 1 D1 is D;
D = Q or K;
Q = -NO or NO2;
K = -Wa-Eb-(C(Re)(Rf))p-Ec-(C(Re)(Rf))x-Wd -(C(Re)(Rf))y-Wi-Ej-Wg-(C(Re)(Rf))z-T-Q;
a, b, c, d, g, i, j = 0-3;
p, x, y, z = 0-10;
E = -T-, alkyl, aryl, (C(Re)(Rf))h-,
W = -C(O)-, -C(S)- or as defined for E;
h = 1 10;
q = 1-5;
Re, Rf = H, alkyl, cycloalkoxy, halo, OH, hydroxyalkyl, alkoxyalkyl, aryl-heterocyclic, alkylaryl, cycloalkylalkyl, heterocyclic-alkyl, alkoxy, haloalkoxy, NH2, alkylamino, dialkylamino, arylamino, diarylamino, alkylarylamino, alkoxyhaloalkyl, haloalkoxy, sulfonic acid, sulfonic ester, alkylsulfonic acid, arylsulfonic acid, arylalkoxy, alkylthio, arylthio, cycloalkylthio, cycloalkenyl, CN, aminoalkyl, aminoaryl, aryl, arylalkyl, alkylaryl, carboxamido, alkylcarboxamido, arylcarboxamido, amidyl, carboxyl, carbamoyl, alkylcarboxylic acid, arylcarboxylic acid, alkylcarbonyl, arylcarbonyl, ester, carboxylic ester, alkylcarboxylic ester, arylcarboxylic ester, haloalkoxy, sulfonamido, alkylsulfonamido, arylsulfonamido, sulfonic ester, a urea, phosphoryl, nitro, -T-Q or -(C(Re)(Rf))k-T-Q; or
Re+Rf+attached C atoms = carbonyl, methanthial, heterocyclic, cycloalkyl or a bridged cycloalkyl;
k = 1-3;
T = a covalent bond, carbonyl, O, -S(O)o- or -N(Ra)Ri-;
o = 0-2;
Ra = a lone pair of electrons, H or alkyl;
Ri = H, alkyl, aryl, alkylcarboxylic acid, arylcarboxylic acid, alkylcarboxylic ester, arylcarboxylic ester, alkylcarboxamido, arylcarboxamido, alkylaryl, alkylsulfinyl, alkylsulfonyl, arylsulfinyl, arylsulfonyl, sulfonamido, carboxamido, carboxylic ester, amino alkyl, amino aryl, -CH2-C(T-Q)(Re)(Rf) or -(N2O2)-M+;
M+ = an organic or inorganic cation;
provided that when Ri is -CH2-C(T-Q)(Re)(Rf) or -(N2O2) M+; or Re or Rf are T-Q or (C(Re)(Rf))k-T-Q, then T-Q can be H, alkyl, alkoxy, alkoxyalkyl, aminoalkyl, OH, heterocyclic or aryl; and provided that when X is -C(O)OD1 and D1 is K, then K is not alkyl or cycloalkyl mononitrate; benzoic acid substituted benzyloxy mononitrate; ethylene glycol mononitrate; polyethylene glycol mononitrate; the regioisomeric esters of glycerol dinitrate and oligomers as disclosed in WO9858910.

INDEPENDENT CLAIMS are included for the following:

(a) compositions and kits comprising (I) and at least 1 compound that donates, transfers or releases nitric oxide, or induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, or is a substrate for nitric oxide synthase, and/or at least 1 vasoactive agent; and

(b) compositions and kits comprising at least 1 prostaglandin and at

least 1 S-nitrosothiol compound, useful for treating sexual dysfunction, a cerebrovascular disorder, cardiovascular disorder, benign prostatic hyperplasia, organ transplants, glaucoma or peptic ulcer, or for inducing an abortion.

ACTIVITY - Vasotropic; Cerebroprotective; Cardiant; Cytostatic; Ophthalmological; Antiulcer; Gynecological; Relaxant.

MECHANISM OF ACTION - Smooth muscle relaxant; Nitric oxide donor; Endothelium-derived relaxing factor agonist.

USE - For treating or preventing sexual dysfunction in males or females, treating a cerebrovascular disorder, cardiovascular disorder, benign prostatic hyperplasia, organ transplants, glaucoma or peptic ulcer, or for inducing an abortion (all claimed).

ADVANTAGE - The combination of a prostaglandin and a S-nitrosothiol gives synergistic results.

Dwg.0/4

L12 ANSWER 11 OF 11 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-063702 [08] WPIDS
DOC. NO. CPI: C2001-017852
TITLE: New fused pyrimidin-7-one derivatives are platelet aggregation inhibitors, anti-vasospastic agents and vasodilators for treating erectile dysfunction.
DERWENT CLASS: B02
INVENTOR(S): BADWAN, A A H; EL-ABADELAH, M M M
PATENT ASSIGNEE(S): (JOPH-N) JORDANIAN PHARM MFG & MEDICAL EQUIP
COUNTRY COUNT: 25
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 1057829	A1	20001206	(200108)*	EN	20
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
EP 1057829	B1	20021120	(200277)	EN	
R: AT BE CH CY DE DK ES FR GB GR IE IT LI LU MC NL PT SE					
DE 69904025	E	20030102	(200310)		
ES 2183500	T3	20030316	(200325)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1057829	A1	EP 1999-850097	19990604
EP 1057829	B1	EP 1999-850097	19990604
DE 69904025	E	DE 1999-604025	19990604
		EP 1999-850097	19990604
ES 2183500	T3	EP 1999-850097	19990604

FILING DETAILS:

PATENT NO	KIND		PATENT NO
DE 69904025	E	Based on	EP 1057829
ES 2183500	T3	Based on	EP 1057829

PRIORITY APPLN. INFO: EP 1999-850097 19990604

AN 2001-063702 [08] WPIDS
AB EP 1057829 A UPAB: 20010207
NOVELTY - Fused pyrimidin-7-one derivatives (I) are new.
DETAILED DESCRIPTION - Fused pyrimidin-7-one derivatives of formula (I) their tautomers, solvates, radiolabeled derivatives and salts, are new.
R0-R6 = H, A, OA, SA, N(A)n (sic), COA, OCOA, SCOA, NHCOA, F, Cl, Br, Oaryl or NR8R9;
A = up to 6C alkyl, hydroxyalkyl or optionally unsaturated cycloalkyl;
n = 1 or 2;
X1, X2 = Cm (optionally substituted by a group R0-R6 and optionally containing a double bond, ketone or thioketone), O, S or NR10;
R8-R10 = A, 1-6C alkylcarbonyl or 1-6C alkoxy; or
NR8R9 = 5 or 6 membered optionally unsaturated ring;
Y = CR11N, N=CR12, N=N, CR13=CR14, CR15R16CR17R18, CR19R20O, OCR21R22, CR23R24NR24, NR25CR26R27 or NR28NR29;
NZ = pyrrolidinyl, piperidinyl, morpholinyl, imidazolyl, pyridinyl, pyrrolyl, or 4-N(R30)-piperazinyl
R11-R30 = a group R0-R6.
ACTIVITY - Vasotropic; Cerebroprotective; Neuroprotective; Antianginal; Hypotensive; Cardiant; Antiarteriosclerotic; Antiasthmatic; Hypotensive; Antiallergic; Ophthalmological.
In tests on rats the ED50 value of 5-(2,3-dihydro-5-(4-methylpiperazin-1-ylsulfonyl)-7-benzofuryl)-1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo(4,3-d)pyrimidin-7-one (Ia) was lower than **sildenafil** (0.2473 mg/kg compared to 0.2843 mg/kg) to elicit an erectile response. The intensity of the erectile response was also superior with (Ia) compared to **sildenafil**.
MECHANISM OF ACTION - None given.
USE - As platelet aggregation inhibitors, anti-vasospastic agents and vasodilators for treating erectile dysfunction (claimed). (I) may also be useful for treating e.g. angina, hypertension, congestive heart failure, peripheral vascular disease, arteriosclerosis, stroke, bronchitis, asthma, allergic rhinitis and **glaucoma**.
Dwg.0/2

(FILE 'HCAPLUS' ENTERED AT 12:55:03 ON 15 OCT 2004)

L1	6	SEA FILE=REGISTRY ABB=ON PLU=ON (NITROGLYCERIN OR ARGININE OR ISOSORBIDE DINITRATE OR SODIUM NITROPRUSSIDE OR PYRIMIDINE)/CN
L2	1	SEA FILE=REGISTRY ABB=ON PLU=ON L-ARGININE/CN
L3	6	SEA FILE=REGISTRY ABB=ON PLU=ON L1 OR L2
L4	1	SEA FILE=REGISTRY ABB=ON PLU=ON SILDENAFIL/CN
L5	149033	SEA FILE=HCAPLUS ABB=ON PLU=ON L3 OR NITROGLYCERIN OR ANGININE OR NITRODERM OR NITRO(W)(DERM OR BID OR DUR OR STAT) OR NITROBID OR NITRODUR OR GLYCERYL(W)(TRINITRATE OR TRI NITRATE) OR GILUSTENON OR NITROSTAT OR TRINITRIN OR ARGININE OR ARG OR (ISOSORBIDE OR (I OR ISO)(W)SORBIDE)(W)(DINITRATE OR DI NITRATE)
L6	12021	SEA FILE=HCAPLUS ABB=ON PLU=ON NITRO(W)(GLYCERIN OR PRUSSIDE OR FERRICYANIDE) OR NITROPRUSSIDE OR NITROFERRICYANIDE OR NANIPRUS OR NIPRUTON OR ISOBID OR ISO BID OR ISODINIT OR DILATRATE OR SORBITRATE OR SORBONIT OR ISORDIL
L7	1134	SEA FILE=HCAPLUS ABB=ON PLU=ON L4 OR SILDENAFIL OR VIAGRA OR (UK 92480 OR UK92480)(W)10

Searcher : Shears 571-272-2528

L8 2 SEA FILE=REGISTRY ABB=ON PLU=ON NITROPRUSSIDE/CN OR "NITROPRUSSIDE SODIUM"/CN
L15 273766 SEA FILE=HCAPLUS ABB=ON PLU=ON L5 OR L6 OR L8 OR PYRIMIDINE OR NO(S)NITRIC OR NITRIC OXIDE
L29 1005 SEA FILE=HCAPLUS ABB=ON PLU=ON (L15 OR NITROGLYCERINE OR NITRO GLYCERINE) AND (L7 OR CGMPPDE# OR ((CGMP OR ((C OR CYCLIC)(W)(GMP OR GUANOSINE))(S)(MONOPHOSPHATE OR MONO PHOSPHATE OR MP))(S)(PDE# OR PHOSPHODIESTERASE OR PHOSPHO(W)(DI ESTERASE OR DI ESTERASE) OR PHOSPHODI ESTERASE)))
L30 10 SEA FILE=HCAPLUS ABB=ON PLU=ON L29 AND ((OCULAR OR OPTIC? OR EYE)(S)(HYPERTENS? OR HYPER TENS? OR (HIGH BLOOD OR HB)(W)PRESSURE OR HBP) OR GLAUCOMA)

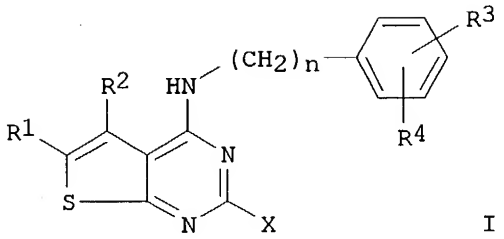
L31 8 L30 NOT L10

L31 ANSWER 1 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 09 Aug 2002
ACCESSION NUMBER: 2002:591553 HCAPLUS
DOCUMENT NUMBER: 137:154940
TITLE: Preparation of thieno[2,3-d]**pyrimidines** as inhibitors of **cGMP**- and cAMP-**phosphodiesterase** (**PDE** V)
INVENTOR(S): Eggenweiler, Hans-Michael; Eiermann, Volker; Schelling, Pierre
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 40 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10104802	A1	20020808	DE 2001-10104802	20010202
WO 2002062343	A2	20020815	WO 2002-EP256	20020114
WO 2002062343	A3	20021121		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1357915	A2	20031105	EP 2002-702259	20020114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2002006853	A	20040113	BR 2002-6853	20020114
JP 2004525890	T2	20040826	JP 2002-562350	20020114
US 2004063731	A1	20040401	US 2003-470763	20030731
PRIORITY APPLN. INFO.:			DE 2001-10104800 A	20010202
			DE 2001-10104801 A	20010202
			DE 2001-10104802 A	20010202
			WO 2002-EP256 W	20020114

Searcher : Shears 571-272-2528

OTHER SOURCE(S): MARPAT 137:154940
GI



I

AB Pharmaceutical formylation containing title compds. [I; R1, R2 = H, A, halo; or R1R2 = C3-5 alkylene; R3,R4 = H, A, OA, OH, halo; or R3R4 = C3-5 alkylene , OCH2CH2, OCH2O, OCH2CH2O; X = (CO2H-, CO2A-, CONH2-, CONHA-, CONA2-, cyano-substituted) (interrupted) alkylene, cycloalkylalkylene, C6H4(CH2)m; A = C1-6 alkyl; m = 1, 2; n = 0-3] and/or salts, and/or solvates thereof, and ≥1 endothelin receptor antagonist, is claimed. Thus, 2.2 g Me 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]benzothieno[2,3-d]pyrimidin-2-yl]propionate (preparation given)
was saponified with 32% NaOH to 2.0 g the corresponding propionic acid which was crystallized with HOCH2CH2NH2 to give 1.35 g 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro-[1]benzothieno[2,3-d]pyrimidin-2-yl]propionic acid ethanolamine salt. I were said to show affinity for **cGMP-** and cAMP-**phosphodiesterase** (**PDE** V) (no data).

L31 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 09 Aug 2002
ACCESSION NUMBER: 2002:591552 HCAPLUS
DOCUMENT NUMBER: 137:154939
TITLE: Preparation of 4-benzylamino[1]benzothieno[2,3-d] **pyrimidines** as inhibitors of **cGMP-** and cAMP-**phosphodiesterase** (**PDE** V)
INVENTOR(S): Eggenweiler, Hans-Michael; Eiermann, Volker; Schelling, Pierre
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 38 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

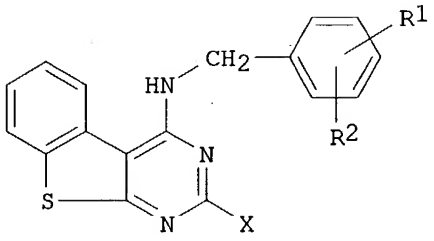
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10104801	A1	20020808	DE 2001-10104801	20010202
WO 2002062343	A2	20020815	WO 2002-EP256	20020114
WO 2002062343	A3	20021121		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR,

LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL,
PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG,
US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1357915	A2	20031105	EP 2002-702259		20020114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
BR 2002006853	A	20040113	BR 2002-6853		20020114
JP 2004525890	T2	20040826	JP 2002-562350		20020114
US 2004063731	A1	20040401	US 2003-470763		20030731
PRIORITY APPLN. INFO.:			DE 2001-10104800	A	20010202
			DE 2001-10104801	A	20010202
			DE 2001-10104802	A	20010202
			WO 2002-EP256	W	20020114

OTHER SOURCE(S): MARPAT 137:154939
GI



I

AB Pharmaceutical formylation containing title compds. [I; R1, R2 = H, A, OA, OH, halo; or R1R2 = C3-5 alkylene, OCH2CH2, CH2OCH2, OCH2O, OCH2CH2O; X = (CO2H-, CO2A-, CONH2-, CONHA-, CONA2-, cyano-substituted) (interrupted) alkylene, cycloalkyl, cycloalkylalkylene, Ph, PhMe; A = C1-6 alkyl] and/or salts, and/or solvates thereof, and ≥1 endothelin receptor antagonist, is claimed. Thus, Me 4-(4-chlorobenzothieno[2,3-d]pyrimidin-2-yl)phenylcarboxylic acid ester was heated at 110° with 3-chloro-4-methoxybenzylamine in N-methylpyrrolidone for 4 h to give ca. 61% Me 4-[4-(3-chloro-4-methoxybenzylamino)[1]benzothieno[2,3-d]pyrimidin-2-yl]benzoate. I were said to show affinity for **cGMP**- and cAMP-**phosphodiesterase** (**PDE** V) (no data).

L31 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 09 Aug 2002
ACCESSION NUMBER: 2002:591551 HCAPLUS
DOCUMENT NUMBER: 137:154938
TITLE: Preparation of pyrazolo[4,3-d]**pyrimidines** as inhibitors of **cGMP**- and cAMP-**phosphodiesterase** (**PDE** V)
INVENTOR(S): Eggenweiler, Hans-Michael; Eiermann, Volker; Schelling, Pierre
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 38 pp.
CODEN: GWXXBX

DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10104800	A1	20020808	DE 2001-10104800	20010202
WO 2002062343	A2	20020815	WO 2002-EP256	20020114
WO 2002062343	A3	20021121		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1357915	A2	20031105	EP 2002-702259	20020114
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2002006853	A	20040113	BR 2002-6853	20020114
JP 2004525890	T2	20040826	JP 2002-562350	20020114
US 2004063731	A1	20040401	US 2003-470763	20030731

PRIORITY APPLN. INFO.:	DE 2001-10104800	A	20010202
	DE 2001-10104801	A	20010202
	DE 2001-10104802	A	20010202
	WO 2002-EP256	W	20020114

OTHER SOURCE(S): MARPAT 137:154938
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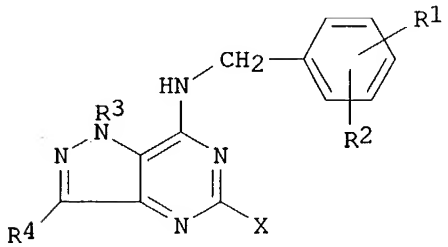


I

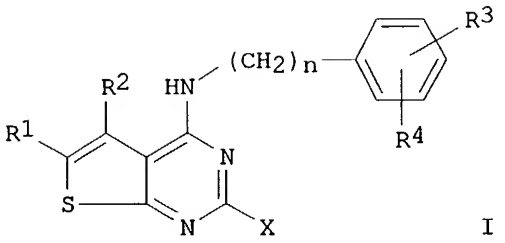
AB Pharmaceutical formylation containing title compds. [I; R1, R2 = H, A, OA, OH, halo; or R1R2 = C3-5 alkylene, OCH2CH2, CH2OCH2, OCH2O, OCH2CH2O; R3, R4 = H, A; X = (CO2H-, CO2A-, CONH2-, CONHA-, CONA2-, cyano-substituted) (interrupted) alkylene, cycloalkyl, cycloalkylalkylene, Ph, PhMe; A = C1-6 alkyl] and/or salts, and/or solvates thereof, and ≥1 endothelin receptor antagonist, is claimed. Thus, Me 4-[7-chloro-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl]phenylcarboxylic acid ester was heated at 110° with 3-chloro-4-methoxybenzylamine in N-methylpyrrolidone for 4 h to give ca. 54% Me 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl]benzoate. I were said to show

affinity for **cGMP**- and cAMP-**phosphodiesterase** (**PDE** V) (no data).

L31 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 02 Aug 2002
ACCESSION NUMBER: 2002:573254 HCAPLUS
DOCUMENT NUMBER: 137:125173
TITLE: Preparation of thieno[2,3-d]**pyrimidines** as inhibitors of **cGMP**- and cAMP-**phosphodiesterase** (**PDE** V)
INVENTOR(S): Eggenweiler, Hans-Michael; Eiermann, Volker; Schelling, Pierre
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 14 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
DE 10104097	A1	20020801	DE 2001-10104097		20010131
WO 2002060449	A2	20020808	WO 2001-EP15324		20011227
WO 2002060449	A3	20030130			
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
EP 1355649	A2	20031029	EP 2001-988079		20011227
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
BR 2001016849	A	20040225	BR 2001-16849		20011227
JP 2004517940	T2	20040617	JP 2002-560641		20011227
US 2004077664	A1	20040422	US 2003-470485		20030730
PRIORITY APPLN. INFO.:			DE 2001-10104095	A	20010131
			DE 2001-10104096	A	20010131
			DE 2001-10104097	A	20010131
			WO 2001-EP15324	W	20011227

OTHER SOURCE(S): MARPAT 137:125173
GI



I

AB Pharmaceutical formylation containing title compds. [I; R1, R2 = H, A, halo; or R1R2 = C3-5 alkylene; or R3, R4 = H, A, OH, OA, halo; or R3R4 = C3-5 alkylene, OCH2CH2, OCH2O, OCH2CH2O; X = (CO2H-, CO2A-, CONH2-, CONHA-, CONA2-, cyano-substituted) (interrupted) alkylene, cycloalkylalkylene, Ph(CH2)m; A = C1-6 alkyl; m = 1, 2; n = 0-3] and salts, solvates, and nitrates thereof for the production of a drug for the treatment of angina, hypertension, pulmonary hypertension, congestive heart failure, chronic obstructive pulmonary disease, cor pulmonale, right ventricular heart failure, atherosclerosis, peripheral blood vessel disease, apoplexia, bronchitis, allergic and chronic asthma, allergic rhinitis, **glaucoma**, irritable bowel syndrome, tumor, kidney insufficiency, and liver cirrhosis, is claimed. Thus, 2.2 g Me 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]propionate (preparation given) in MeOCH2CH2OH was saponified with NaOH to give 2.0 g 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]propionic acid which was crystallized with HOCH2CH2NH2 to give 1.35 g 3-[4-(3-chloro-4-methoxybenzylamino)-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-2-yl]propionic acid ethanolamine salt. I were said to have affinity to **cGMP**- and cAMP-**phosphodiesterase** (**PDE** V) (no data).

IT **55-63-0**, Glycerol trinitrate **87-33-2**, **Isosorbide dinitrate**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of thienopyrimidines as inhibitors of **cGMP**- and cAMP-**phosphodiesterase** (**PDE** V))

L31 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 02 Aug 2002
ACCESSION NUMBER: 2002:573253 HCAPLUS
DOCUMENT NUMBER: 137:125172
TITLE: Preparation of 4-(benzylamino)[1]benzothieno[2,3-d] **pyrimidines** as inhibitors of **cGMP**- and cAMP-**phosphodiesterase** (**PDE** V)
INVENTOR(S): Eggenweiler, Hans-Michael; Eiermann, Volker; Schelling, Pierre
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 12 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10104096	A1	20020801	DE 2001-10104096	20010131
WO 2002060449	A2	20020808	WO 2001-EP15324	20011227
WO 2002060449	A3	20030130		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1355649	A2	20031029	EP 2001-988079	20011227
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001016849	A	20040225	BR 2001-16849	20011227
JP 2004517940	T2	20040617	JP 2002-560641	20011227
US 2004077664	A1	20040422	US 2003-470485	20030730
PRIORITY APPLN. INFO.:			DE 2001-10104095 A	20010131
			DE 2001-10104096 A	20010131
			DE 2001-10104097 A	20010131
			WO 2001-EP15324 W	20011227

OTHER SOURCE(S): MARPAT 137:125172

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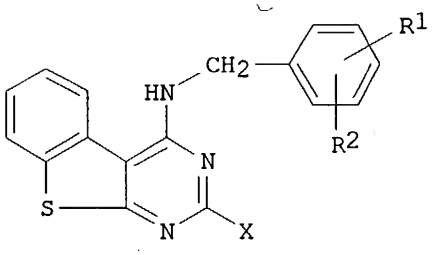

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methoxybenzylamino)[1]benzothieno[2,3-d]pyrimidin-2-yl]benzoate. I were said to have affinity to **cGMP**- and cAMP-**phosphodiesterase** (**PDE** V) (no data).

IT **55-63-0**, Glycerol trinitrate **87-33-2**, **Isosorbide dinitrate**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of (benzylamino)benzothienopyrimidines as inhibitors of **cGMP**- and cAMP-**phosphodiesterase** (**PDE** V))

L31 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 02 Aug 2002
ACCESSION NUMBER: 2002:573252 HCAPLUS
DOCUMENT NUMBER: 137:125171
TITLE: Preparation of 4-(benzylamino)-1H-pyrazolo[4,3-d] **pyrimidines** as inhibitors of **cGMP**- and cAMP-**phosphodiesterase** (**PDE** V)
INVENTOR(S): Eggenweiler, Hans-Michael; Eiermann, Volker; Schelling, Pierre
PATENT ASSIGNEE(S): Merck Patent G.m.b.H., Germany
SOURCE: Ger. Offen., 12 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 10104095	A1	20020801	DE 2001-10104095	20010131
WO 2002060449	A2	20020808	WO 2001-EP15324	20011227
WO 2002060449	A3	20030130		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1355649	A2	20031029	EP 2001-988079	20011227
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
BR 2001016849	A	20040225	BR 2001-16849	20011227
JP 2004517940	T2	20040617	JP 2002-560641	20011227
US 2004077664	A1	20040422	US 2003-470485	20030730

PRIORITY APPLN. INFO.:

DE 2001-10104095	A	20010131
DE 2001-10104096	A	20010131
DE 2001-10104097	A	20010131
WO 2001-EP15324	W	20011227

OTHER SOURCE(S): MARPAT 137:125171
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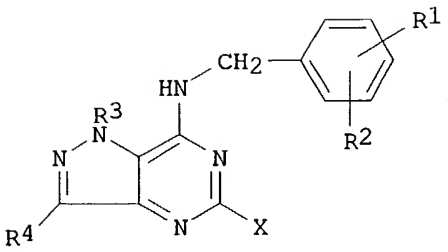

I

AB Pharmaceutical formylation containing title compds. [I; R1, R2 = H, A, OA, OH,
halo; or R1R2 = C3-5 alkylene, OCH2CH2, CH2OCH2, OCH2O, OCH2CH2O; R3, R4 = H, A; X = (CO2H-, CO2A-, CONH2-, CONHA-, CONA2-, cyano-substituted) (interrupted) alkylene, cycloalkyl, cycloalkylalkylene, Ph, PhMe; A = C1-6 alkyl] and salts, solvates, and nitrates thereof for the production of a drug
for the treatment of angina, hypertension, pulmonary hypertension, congestive heart failure, chronic obstructive pulmonary disease, cor pulmonale, right ventricular heart failure, atherosclerosis, peripheral blood vessel disease, apoplexia, bronchitis, allergic and chronic asthma, allergic rhinitis, **glaucoma**, irritable bowel syndrome, tumor, kidney insufficiency, and liver cirrhosis, is claimed. Thus, Me 4-[7-chloro-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-2-yl]phenylcarboxylic acid ester was heated at 110° with 3-chloro-4-methoxybenzylamine in N-methylpyrrolidone for 4 h to give ca. 54% Me 4-[7-(3-chloro-4-methoxybenzylamino)-1-methyl-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-2-yl]benzoate. I were said to have affinity to **cGMP**- and cAMP-**phosphodiesterase** (**PDE** V) (no data).

IT **55-63-0**, Glycerol trinitrate **87-33-2**, **Isosorbide dinitrate**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(preparation of (benzylamino)pyrazolopyrimidines as inhibitors of **cGMP**- and cAMP-**phosphodiesterase** (**PDE** V))

L31 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 09 Nov 2000
ACCESSION NUMBER: 2000:785898 HCAPLUS
DOCUMENT NUMBER: 133:329627
TITLE: Tetracyclic **cGMP**-specific **phosphodiesterase** inhibitors and their use in disease treatment
INVENTOR(S): Daugan, Alain Claude Marie; Gellibert, Francoise
PATENT ASSIGNEE(S): Icos Corp., USA
SOURCE: U.S., 30 pp., Cont.-in-part of PCT 9519978.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6143746	A	20001107	US 1998-154051	19980916
WO 9519978	A1	19950727	WO 1995-EP183	19950119
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US				
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
WO 9703675	A1	19970206	WO 1996-EP3024	19960711
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG				
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WO 9703985	A1	19970206	WO 1996-EP3025	19960711
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US 6025494	A	20000215	US 1998-133078	19980812
CA 2340636	AA	20000323	CA 1999-2340636	19990826
EP 1113800	A1	20010711	EP 1999-945201	19990826
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002524516	T2	20020806	JP 2000-569812	19990826
US 6127542	A	20001003	US 1999-399667	19990921
US 6369059	B1	20020409	US 2000-633431	20000807
CZ 289832	B6	20020417	CZ 2000-3428	20000919
US 2002119976	A1	20020829	US 2002-68114	20020205
US 6784179	B2	20040831		
JP 2004217674	A2	20040805	JP 2004-125881	20040421

PRIORITY APPLN. INFO.:		
GB 1994-1090	A	19940121
WO 1995-EP183	A2	19950119
GB 1995-14464	A	19950714
GB 1995-14465	A	19950714
WO 1996-EP3024	A2	19960711
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JP 1995-519339	A3	19950119
CZ 1998-33	A3	19960711
US 1996-669389	A3	19960716
US 1998-133078	A1	19980812
US 1998-154051	A	19980916
WO 1999-US19466	W	19990826
US 1999-399667	A1	19990921
US 2000-633431	A1	20000807

OTHER SOURCE(S): MARPAT 133:329627

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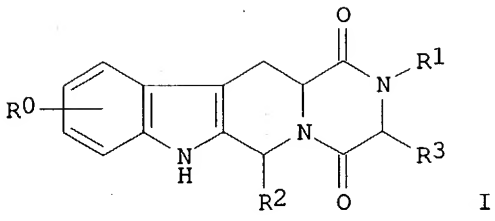
Searcher : Shears 571-272-2528



I

AB A compound of formula I (R0 = H, halogen, C1-6 alkyl; R1 = H, C1-6 alkyl, C2-6 alkenyl, C2-6 alkynyl, halo-C1-6 alkyl, C3-8 cycloalkyl, C3-8 cycloalkyl-C1-3 alkyl, aryl-C1-3 alkyl, heteroaryl-C1-3 alkyl; R2 = (substituted) monocyclic aromatic ring selected from benzene, thiophene, furan, and pyridine, or (substituted) bicyclic ring (a) attached to the rest of the mol. via one of the benzene ring carbon atoms, and wherein the fused ring is a 5- or 6-membered ring which may be saturated or partially or fully unsatd., and comprises carbon atoms and optionally one or two heteroatoms selected from oxygen, sulfur, and nitrogen; R3 = H, C1-3 alkyl, or R1 and R3 together = 3- or 4-membered alkyl or alkenyl chain) and salts and solvates thereof is disclosed. Compound I is a potent and selective inhibitor of **cyclic guanosine** 3',5'-**monophosphate**-specific **phosphodiesterase**, having a utility in a variety of therapeutic areas where such inhibition is beneficial, including the treatment of cardiovascular disorders and erectile dysfunction. Thus, many I compds. were synthesized and tested in vitro as inhibitors of **cGMP phosphodiesterase**. Cis-2,3,6,7,12,12a-hexahydro-2-(4-pyridylmethyl)-6-(3,4-methylenedioxyphenyl)pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione showed IC50 of 10 nM.

IT **55-63-0, Nitroglycerin 87-33-2, Isosorbide dinitrate 14402-89-2**, Sodium **nitroprusside**
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(drug containing phosphodiesterase inhibitor and; tetracyclic cyclic GMP-specific phosphodiesterase inhibitors and their use in disease treatment)

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L31 ANSWER 8 OF 8 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 04 Mar 1989
ACCESSION NUMBER: 1989:69411 HCAPLUS
DOCUMENT NUMBER: 110:69411
TITLE: Atriopeptins, guanylate cyclase activators, and phosphodiesterase inhibitors for treatment of **glaucoma**, hydrocephalus, and cerebral edema (cranial fluid volume dysfunction)
INVENTOR(S): Nathanson, James A.
PATENT ASSIGNEE(S): General Hospital Corp., USA
SOURCE: PCT Int. Appl., 75 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 8805306	A1	19880728	WO 1988-US168	19880122
W: JP				
RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE				
EP 341264	A1	19891115	EP 1988-901976	19880122
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
JP 02502635	T2	19900823	JP 1988-501881	19880122
JP 2845913	B2	19990113		
CA 1319099	A1	19930615	CA 1988-557141	19880122
EP 583821	A1	19940223	EP 1993-202327	19880122
EP 583821	B1	20000329		
R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE				
AT 191145	E	20000415	AT 1993-202327	19880122
US 5500230	A	19960319	US 1993-43979	19930407
PRIORITY APPLN. INFO.:			US 1987-6405	19870123
			US 1988-147324	19880122
			WO 1988-US168	19880122
			US 1990-702855	19901121

AB A method of treating cranial fluid volume dysfunctions such as edema, hydrocephalus, or **glaucoma** comprises administering compds. which increase cGMP at the site of the dysfunction or at the site of synthesis or removal of the accumulating fluid. Intravitreal administration of 0.3 nmol rat atrial natriuretic peptide 1-28 decreased the intraocular pressure in rabbits for 48 h, more in the ipsilateral than in the contralateral eye.

IT **55-63-0, Nitroglycerine**
RL: BIOL (Biological study)
(**glaucoma** and hydrocephalus and cerebral edema treatment with)

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 13:12:19 ON 15 OCT 2004)
L32 30 S L30
L33 19 S L32 NOT L11
L34 19 DUP REM L33 (0 DUPLICATES REMOVED)

L34 ANSWER 1 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2004334118 EMBASE
TITLE: New oral drugs for erectile dysfunction.
SOURCE: Drug and Therapeutics Bulletin, (2004) 42/7 (49-52).
Refs: 21
ISSN: 0012-6543 CODEN: DRTBAE
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 028 Urology and Nephrology
030 Pharmacology
036 Health Policy, Economics and Management
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

Searcher : Shears 571-272-2528

AB In 1998, we concluded that **sildenafil** (**Viagra** - Pfizer Ltd), a selective phosphodieste rase type 5 inhibitor, appeared to offer advantages over other medical approaches for erectile dysfunction in terms of ease of administration and cost. Oral drug treatment is now widely advocated as first-line therapy for erectile dysfunction, except where the cause isclearly psychological. In the past 4 years, three more oral preparations have been licensed in the UK for the treatment of men with erectile dysfunction. A sublingual preparation of the dopaminergic agonist apomorphine (Uprima - Abbott Laboratories Ltd) is the first centrally acting drug to be licensed. Tadalafil (Cialis - Eli-Lilly) and vardenafil (Levitra - Bayer PLC) are phosphodiesterase type 5 inhibitors. Here we review the place of these preparations for men with erectile dysfunction.

L34 ANSWER 2 OF 19 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2003078515 EMBASE

TITLE: Incubation of porcine iris-ciliary bodies to study the mechanisms by which **nitric oxide** donors lower intraocular pressure.

AUTHOR: Kotikoski H.; Kankuri E.; Vapaatalon H.

CORPORATE SOURCE: Dr. H. Vapaatalon, Institute of Biomedicine, Biomedicum Helsinki, University of Helsinki, P.O. Box 63, Helsinki FIN-00014, Finland. heikki.vapaatalo@helsinki.fi

SOURCE: Medical Science Monitor, (1 Jan 2003) 9/1 (BR1-BR7). Refs: 36
ISSN: 1234-1010 CODEN: MSMOFR

COUNTRY: Poland

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 012 Ophthalmology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Background: We previously reported that several **nitric oxide** (**NO**) donors, guanylate cyclase activators, and cyclic GMP lower intraocular pressure (IOP) in rabbits. Material/Methods: This study evaluated a novel method for studying **cGMP** production in the iris-ciliary body after the administration of different **NO** donors and guanylate cyclase activators. Tissue samples of porcine iris-ciliary body were incubated for 30 or 60 minutes with the test compounds and with or without the **phosphodiesterase** inhibitor zaprinast. The concentration of **cGMP** in the iris-ciliary body as an indicator of soluble guanylate cyclase activation was measured by radioimmunoassay. Results: The tested **NO** donors - SNOG, NONOate, NOR-3, and SNAP - were shown to release **NO** in incubation medium, and clearly increase **cGMP** concentration in the iris-ciliary body. Cyclic GMP production was 2-5 times higher with nitrosocaptopril and about 10 times higher with SNP than in the unstimulated control tissue incubation. Captopril, the reference for nitrosocaptopril, did not induce **cGMP** production in the porcine iris-ciliary body. ODQ, a guanylate cyclase inhibitor, shut down the production of **cGMP** after the administration of nitrosocaptopril and SNP. The guanylate cyclase activators YC-1 and atriopeptin III increased **cGMP** dose-dependently. Conclusion: In this novel tissue incubation method, several **NO** donors and guanylate cyclase activators increased

cGMP production in the porcine iris-ciliary body. This method can be used to screen new molecules in terms of **cGMP** production, since the ciliary body is important in lowering intraocular pressure.

L34 ANSWER 3 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-682945 [73] WPIDS
DOC. NO. CPI: C2002-192776
TITLE: New pyrazolo-4,3-D-**pyrimidine** derivatives useful in the treatment/prevention of a medical condition e.g. male erectile dysfunction.
DERWENT CLASS: B02
INVENTOR(S): ALLERTON, C M N
PATENT ASSIGNEE(S): (ALLE-I) ALLERTON C M N; (PFIZ) PFIZER INC; (PFIZ) PFIZER LTD
COUNTRY COUNT: 99
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002072586	A1	20020919	(200273)*	EN	52
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
US 2002173502	A1	20021121	(200279)		
AU 2002234832	A1	20020924	(200433)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002072586	A1	WO 2002-IB622	20020227
US 2002173502	A1 Provisional	US 2001-291714P	20010517
		US 2002-92992	20020306
AU 2002234832	A1	AU 2002-234832	20020227

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2002234832	A1 Based on	WO 2002072586

PRIORITY APPLN. INFO: GB 2001-5893 20010309
AN 2002-682945 [73] WPIDS
AB WO 200272586 A UPAB: 20021113
NOVELTY - Pyrazolo-4,3-D-**pyrimidine** derivatives (I), their salts, polymorphs and/or solvates are new.

DETAILED DESCRIPTION - Pyrazolo-4,3-D-**pyrimidine** derivatives of formula (I), their salts, polymorphs and/or solvates are new.

R1 = H, C(O)1-4C alkyl or C(O)(hetero)aryl.

ACTIVITY - Vasotropic; Analgesic; Gynecological; Analgesic; Cytostatic; Uropathic; Antianginal; Cardiant; Antiarteriosclerotic; Cerebroprotective; Antiinflammatory; Antiallergic; Antiasthmatic;

Opthalmological; Immunomodulator; Dermatological; Neuroprotective; Antidiabetic; Nootropic; Antipsoriatic; Hypotensive; Endocrine.

MECHANISM OF ACTION - **Cyclic guanosine** 3',5'-**monophosphate** (GMP) **phosphodiesterase** (**PDE**) inhibitor.

PDE inhibition was assayed using a fixed amount of enzyme in the presence of 5-(2-butoxy-5-(1-hydroxyethyl)-3-pyridinyl)-3-ethyl-2-(1-ethyl-3-azetidinyl)-2,6-dihydro-7H-pyrazolo(4,3-d)pyrimidin-7-one (Ia) in varying concentrations and low substrate, (**cGMP** or cAMP in a 3:1 ratio unlabelled to (3H)-labeled at a concentration approx. 1/3 Km). The final assay volume was made up to 100 micro l with assay buffer (Tris-HCl (20 mM), pH 7.4, MgCl2 (5 mM), bovine serum albumin (1 mg/ml)). Reactions were initiated with enzyme, incubated for 30 - 60 minutes at 30 deg. C to give less than 30% substrate turnover and terminated with 50 micro l yttrium silicate SPA beads. Plates were re-sealed and shaken for 20 minutes, after which the beads were allowed to settle for 30 minutes in the dark and then counted. The IC50 value of (Ia) was found to be 0.825 micro M.

USE - For use in the manufacture of a medicament for the curative or prophylactic treatment of a medical condition for which inhibition of **cGMP PDE5** is desired; for use in pharmaceutical formulation (preferably veterinary formulation) or in an animal medicament; for treating or preventing a medical condition for which inhibition of **cGMP PDE5** is desired (e.g. male erectile dysfunction (MED), impotence, female sexual dysfunction (FSD), clitorial dysfunction, female hypoactive sexual desire disorder, female sexual arousal disorder, female sexual pain disorder or female sexual orgasmic dysfunction (FSOD)) (all claimed). Also useful in treating conditions e.g. premature labor, dysmenorrhea, benign prostatic hyperplasia (BPH), bladder outlet obstruction, incontinence, stable angina, unstable angina, variant (Prinzmetal) angina, **hypertension**, pulmonary **hypertension**, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, atherosclerosis, post-percutaneous transluminal coronary angioplasty (post-PTCA), peripheral vascular disease, stroke, nitrate induced tolerance, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, **glaucoma**, **optic** neuropathy, macular degeneration, elevated intra-occular pressure, retinal or arterial occlusion, irritable bowel syndrome (IBS), pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, diabetic neuropathy, autonomic neuropathy, peripheral neuropathy, gastroparesis, peripheral diabetic neuropathy, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer, metastasis, baldness, nutcracker esophagus, anal fissure, hemorrhoids, hypotoxic vasoconstriction, diabetes, type 2 diabetes mellitus, the insulin resistance syndrome, insulin resistance, impaired glucose tolerance, stabilization of blood pressure during hemodialysis.

ADVANTAGE - (I) is more effective, less toxic, have a broader range of activity, produce fewer side effects and more easily absorbed.

Dwg.0/0

L34 ANSWER 4 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-292192 [33] WPIDS
DOC. NO. CPI: C2002-085867
TITLE: New tetrahydro-benzothieno-**pyrimidine** derivatives are phosphodiesterase V inhibitors useful e.g. for treating cardiovascular disorders or impotence.

DERWENT CLASS: B02
INVENTOR(S): BEIER, N; CHRISTADLER, M; EGGENWEILER, H; JONAS, R; SCHELLING, P; EGGENWEILER, H M; ROCHUS, J
PATENT ASSIGNEE(S): (MERE) MERCK PATENT GMBH; (BEIE-I) BEIER N; (CHRI-I) CHRISTADLER M; (EGGE-I) EGGENWEILER H; (JONA-I) JONAS R; (SCHE-I) SCHELLING P
COUNTRY COUNT: 97
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002018389	A2	20020307	(200233)*	GE	33
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
DE 10042997	A1	20020314	(200233)		
AU 2001093719	A	20020313	(200249)		
NO 2003000948	A	20030228	(200334)		
CZ 2003000794	A3	20030618	(200347)		
SK 2003000337	A3	20030701	(200352)		
KR 2003032000	A	20030423	(200353)		
BR 2001013582	A	20030715	(200365)		
US 2003187260	A1	20031002	(200365)		
EP 1351962	A2	20031015	(200368)	GE	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
MX 2003001773	A1	20030601	(200417)		
HU 2003003677	A2	20040428	(200435)		
JP 2004519426	W	20040702	(200443)		61
US 6780867	B2	20040824	(200457)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002018389	A2	WO 2001-EP8998	20010803
DE 10042997	A1	DE 2000-10042997	20000901
AU 2001093719	A	AU 2001-93719	20010803
NO 2003000948	A	WO 2001-EP8998	20010803
		NO 2003-948	20030228
CZ 2003000794	A3	WO 2001-EP8998	20010803
		CZ 2003-794	20010803
SK 2003000337	A3	WO 2001-EP8998	20010803
		SK 2003-337	20010803
KR 2003032000	A	KR 2003-703006	20030228
BR 2001013582	A	BR 2001-13582	20010803
		WO 2001-EP8998	20010803
US 2003187260	A1	WO 2001-EP8998	20010803
		US 2003-362993	20030303
EP 1351962	A2	EP 2001-974106	20010803
		WO 2001-EP8998	20010803
MX 2003001773	A1	WO 2001-EP8998	20010803
		MX 2003-1773	20030227

Searcher : Shears 571-272-2528

HU 2003003677	A2	WO 2001-EP8998	20010803
		HU 2003-3677	20010803
JP 2004519426	W	WO 2001-EP8998	20010803
		JP 2002-523904	20010803
US 6780867	B2	WO 2001-EP8998	20010803
		US 2003-362993	20030303

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001093719	A Based on	WO 2002018389
CZ 2003000794	A3 Based on	WO 2002018389
SK 2003000337	A3 Based on	WO 2002018389
BR 2001013582	A Based on	WO 2002018389
EP 1351962	A2 Based on	WO 2002018389
MX 2003001773	A1 Based on	WO 2002018389
HU 2003003677	A2 Based on	WO 2002018389
JP 2004519426	W Based on	WO 2002018389
US 6780867	B2 Based on	WO 2002018389

PRIORITY APPLN. INFO: DE 2000-10042997 20000901

AN 2002-292192 [33] WPIDS

AB WO 200218389 A UPAB: 20030211

NOVELTY - 4-Benzylamino-5,6,7,8-tetrahydro-benzo (4,5) thieno (2,3-d) **pyrimidine** derivatives (I) are new.

DETAILED DESCRIPTION - 4-Benzylamino-5,6,7,8-tetrahydro-benzo (4,5) thieno (2,3-d) **pyrimidine** derivatives of formula (I) and their salts and/or solvates are new.

R1, R2 = H, A, OH, OA, NO2 or halo, or

R1 + R2 = 3-5C alkylene, OCH2CH2, CH2OCH2, OCH2O or OCH2CH2O;

X = R3 or R4, both monosubstituted by R5;

R3 = 1-10C alkylene (optionally having 1 or 2 CH2 groups replaced by CH=CH, O, NH or NA);

R4 = 5-12C cycloalkyl or 5-12C cycloalkylalkylene;

R5 = Q(CH2)nCOOH, Q(CH2)nCOOA, Q(CH2)nCONH2, O(CH2)nCONHA, Q(CH2)nCONA2 or Q(CH2)nCN;

Q = O or S(O)m;

m = 0-2;

n = 1 or 2, and

A = 1-6C alkyl.

(N.B. In dependent claims, A can also be CF3). An INDEPENDENT CLAIM is included for the preparation of (I).

ACTIVITY - Cardiant; Vasotropic; Antianginal; Hypotensive; Antiarteriosclerotic; Cerebroprotective; Antiinflammatory; Antiasthmatic; Antiallergic; Ophthalmological; Cytostatic; Nephrotropic; Hepatotropic.

MECHANISM OF ACTION - **Phosphodiesterase** V (**cGMP phosphodiesterase**) inhibitor.

USE - Used for treating cardiovascular diseases, impotence, angina, hypertension, congestive heart failure, atherosclerosis, pulmonary hypertension, conditions of reduced cardiac blood vessel permeability, peripheral vascular disease, stroke, bronchitis, allergic or chronic asthma, allergic rhinitis, **glaucoma**, irritable bowel syndrome, tumors, renal insufficiency, liver cirrhosis or female sexual disorders (all claimed). They are especially useful for treating cardiac insufficiency or impotence (erectile dysfunction). (I) may also be useful

as intermediates for other drugs.
ADVANTAGE - (I) Are well tolerated, specific phosphodiesterase V inhibitors.
Dwg.0/0

L34 ANSWER 5 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-220128 [21] WPIDS
DOC. NO. CPI: C2003-055912
TITLE: Method for lowering **ocular hypertension** involves administering a **eye** drop containing a combination of **nitric oxide** releasing agent and a **cyclic guanosine**-3',5'-**monophosphate** specific **phosphodiesterase** type 5 inhibitor.
DERWENT CLASS: B03 B05 D16
INVENTOR(S): SHAHINPOOR, M; SHAHINPOOR, P; SOLTANPOUR, D
PATENT ASSIGNEE(S): (SHAH-I) SHAHINPOOR M
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 2002168424	A1	20021114	(200321)*		6

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 2002168424	A1	US 2002-64627	20020731

PRIORITY APPLN. INFO: US 2002-64627 20020731
AN 2003-220128 [21] WPIDS
AB US2002168424 A UPAB: 20030328
NOVELTY - Method for lowering **ocular hypertension** involves administering a topical ophthalmic **eye** drop or ointment containing a combination (weight%) of **nitric oxide** (**NO**) releasing agent or **NO** donor and a **cyclic guanosine**-3',5'-**monophosphate** (**c-GMP**) specific **phosphodiesterase** type 5 (**PDE5**) inhibitor.
ACTIVITY - Hypotensive; Ophthalmological.
MECHANISM OF ACTION - **Cyclic guanosine**-3',5'-**monophosphate** (**c-GMP**) enhancer; **Phosphodiesterase** type 5 (**PDE5**) production inhibitor.
USE - For the treatment of **ocular hypertension** (claimed) and **glaucoma**.
ADVANTAGE - The method can synergistically enhance the aqueous humor outflow, ocular hypotensive and blood circulation to the optic nerve and lowers intraoccular pressure.
Dwg.0/0

L34 ANSWER 6 OF 19 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
ACCESSION NUMBER: 2002:843290 SCISEARCH
THE GENUINE ARTICLE: 601HK
TITLE: **Viagra**((R)) (**sildenafil** citrate) and

ophthalmology
AUTHOR: Laties A M (Reprint); Zrenner E
CORPORATE SOURCE: Univ Penn, Sch Med, Scheie Eye Inst, Dept Ophthalmol, Myrin Circle, 51 N 39th St, Philadelphia, PA 19104 USA (Reprint); Univ Penn, Sch Med, Scheie Eye Inst, Dept Ophthalmol, Philadelphia, PA 19104 USA; Univ Tubingen, Hosp Eye, Dept Pathophysiol Vis & Neurophthalmol, Tubingen, Germany
COUNTRY OF AUTHOR: USA; Germany
SOURCE: PROGRESS IN RETINAL AND EYE RESEARCH, (SEP 2002) Vol. 21, No. 5, pp. 485-506.
Publisher: PERGAMON-ELSEVIER SCIENCE LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, ENGLAND.
ISSN: 1350-9462.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 108

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Viagra**((R)) (**sildenafil** citrate) improves penile erections in men with erectile dysfunction (ED) by selectively inhibiting **cGMP**-specific **phosphodiesterase** type 5 (**PDE5**), which is present in all vascular tissue. It also exerts a minor inhibitory action against **PDE6**, which is present exclusively in rod and cone photoreceptors. At higher doses, **sildenafil** causes mild and transient visual symptoms in a minority of patients (mainly blue tinge to vision, increased brightness of lights). Therefore, the effects of **sildenafil** on the visual system have been investigated in a wide variety of clinical and preclinical studies. In preclinical studies, **sildenafil** shows transient reversible effects on electrical response to light. In long-term toxicology studies in which animals were exposed to high multiples of the maximum human therapeutic dose, detailed examinations have revealed no adverse effects on the structure or function of the eye. The effects of **sildenafil** have been systematically investigated in visual function studies in volunteers and in patients with eye disease; **sildenafil** does not affect visual acuity, visual fields, and contrast sensitivity. The only definite effect is transient, mild impairment of color discrimination occurring around the time of peak plasma levels. In long-term studies, no long-term effects of **sildenafil** on the visual system have been observed. Postmarketing, **sildenafil** has been prescribed to over 15 million men with ED. Isolated examples of a variety of visual adverse events have been reported. No consistent pattern has emerged to suggest any long-term effect of **sildenafil** on the retina or other structures of the eye. Based on this experience, intermittent, short-term, partial inhibition of **PDE5** or **PDE6** by **sildenafil** is unlikely to induce any long-term visual change. (C) 2002 Elsevier Science Ltd. All rights reserved.

L34 ANSWER 7 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-281960 [29] WPIDS
CROSS REFERENCE: 2002-181011 [24]
DOC. NO. CPI: C2001-085893
TITLE: New 5-(pyrid-3-yl)dihydropyrazolo(4,3-d)pyrimidin-7-one compounds are **cGMP PDE5** inhibitors, useful for treating e.g. sexual dysfunction, cardiovascular, optic, and allergic disorders, and

cancer.

DERWENT CLASS: B02

INVENTOR(S): ALLERTON, C M N; BARBER, C G; MAW, G N; RAWSON, D J; DEVRIES, K M; HARRIS, L J; LEVETT, P C; NEGRI, J T; WOOD, A S; ALLERTON, C; NORFOR, M

PATENT ASSIGNEE(S): (ALLE-I) ALLERTON C M N; (BARB-I) BARBER C G; (DEVR-I) DEVRIES K M; (HARR-I) HARRIS L J; (LEVE-I) LEVETT P C; (NEGR-I) NEGRI J T; (RAWS-I) RAWSON D J; (WOOD-I) WOOD A S; (PFIZ) PFIZER INC; (PFIZ) PFIZER LTD

COUNTRY COUNT: 95

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001027112	A1	20010419	(200129)*	EN	204
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000075479	A	20010423	(200147)		
US 2002038024	A1	20020328	(200225)		
CN 1335317	A	20020213	(200233)		
BR 2000014695	A	20020618	(200249)		
NO 2002001695	A	20020607	(200250)		
EP 1222190	A1	20020717	(200254)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
KR 2002010102	A	20020202	(200254)		
HU 2001003075	A2	20020729	(200258)		
KR 2002038941	A	20020524	(200275)		
CN 1378547	A	20021106	(200316)		
HU 2002003438	A2	20030128	(200323)		
CZ 2002001151	A3	20030312	(200324)		
JP 2003511452	W	20030325	(200330)		225
SK 2002000456	A3	20030401	(200331)		
ZA 2002002723	A	20030625	(200348)		221
NZ 517324	A	20030926	(200366)		
MX 2002003629	A1	20020801	(200367)		
US 6756373	B1	20040629	(200443)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2001027112	A1		WO 2000-IB1430	20001004
AU 2000075479	A		AU 2000-75479	20001004
US 2002038024	A1	Provisional	US 2001-276532P	20010316
		Provisional	US 2001-292378P	20010521
			US 2001-916099	20010726
CN 1335317	A		CN 2001-124351	20010727
BR 2000014695	A		BR 2000-14695	20001004
			WO 2000-IB1430	20001004
NO 2002001695	A		WO 2000-IB1430	20001004
			NO 2002-1695	20020410

Searcher : Shears 571-272-2528

EP 1222190	A1		EP 2000-964557	20001004
			WO 2000-IB1430	20001004
KR 2002010102	A		KR 2001-45414	20010727
HU 2001003075	A2		HU 2001-3075	20010727
KR 2002038941	A		KR 2002-704589	20020410
CN 1378547	A		CN 2000-814083	20001004
HU 2002003438	A2		WO 2000-IB1430	20001004
			HU 2002-3438	20001004
CZ 2002001151	A3		WO 2000-IB1430	20001004
			CZ 2002-1151	20001004
JP 2003511452	W		WO 2000-IB1430	20001004
			JP 2001-530330	20001004
SK 2002000456	A3		WO 2000-IB1430	20001004
			SK 2002-456	20001004
ZA 2002002723	A		ZA 2002-2723	20020408
NZ 517324	A		NZ 2000-517324	20001004
			WO 2000-IB1430	20001004
MX 2002003629	A1		WO 2000-IB1430	20001004
			MX 2002-3629	20020410
US 6756373	B1	Provisional	US 2000-231411P	20000908
			US 2000-684228	20001006

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000075479	A	Based on	WO 2001027112
BR 2000014695	A	Based on	WO 2001027112
EP 1222190	A1	Based on	WO 2001027112
HU 2002003438	A2	Based on	WO 2001027112
CZ 2002001151	A3	Based on	WO 2001027112
JP 2003511452	W	Based on	WO 2001027112
SK 2002000456	A3	Based on	WO 2001027112
NZ 517324	A	Based on	WO 2001027112
MX 2002003629	A1	Based on	WO 2001027112

PRIORITY APPLN. INFO: GB 2000-18660 20000728; GB
1999-24041 19991011; GB
2001-7526 20010326; GB
2001-10251 20010426

AN 2001-281960 [29] WPIDS
CR 2002-181011 [24]
AB WO 200127112 A UPAB: 20040709
NOVELTY - 5-(2-Alkoxypyrid-3-yl)dihydropyrazolo(4,3-d)pyrimidin-7-ones and their 2-alkylamino analogs (I) are new.

DETAILED DESCRIPTION - 5-(2-Alkoxypyrid-3-yl)dihydropyrazolo (4,3-d)pyrimidin-7-ones of formula (I) and their 2-alkylamino analogs, both of formula (I), together with their salts and solvates are new:

X = O or NR5;

R1 = H, or 1-6C alkyl, 6-10C aryl, aryl 1-6C alkyl, Het, or Het 1-6C alkyl (all optionally substituted by W);

Het = 4-12 membered ring systems containing heteroatoms from N, O, S, and may be saturated, partially unsaturated, or heteroaryl;

W = halogen, cyano, nitro, 1-6C alkyl or haloalkyl, OR6, OCOR7, COR8, COOR9, CONR10R11, NR12R13, or SO2NR14R15;

R2 = H, W, or 1-6C alkyl, 6-10C aryl, aryl 1-6C alkyl, Het, or Het

1-6C alkyl (all from alkyl optionally substituted by W);
R3 = H, or 1-6C alkyl, 6-10C aryl 1-6C alkyl, or Het 1-6C alkyl (all optionally substituted by W);
R4 = H, W (except SO2NR14R15 and 1-6C alkyl), NR16Y(O)R17, N(Y(O)R17)2, SOR18, SO2R19, C(O)AZ, or 1-6C alkyl, 2-6C alkenyl or alkynyl, Het, Het 1-6C alkyl, aryl, or aryl 1-6C alkyl (all from alkyl optionally substituted by W);
Y = C or SO;
A = 1-6C alkylene;
Z = OR6, halogen, or Het or aryl (both optionally substituted by W);
R5-R9 = H or 1-6C alkyl;
R10, R11 = H or 1-6C alkyl, aryl, or Het (all optionally substituted by W (replacing the definition CONR10 R11 the definition CONR10aR11a) or NR20SO2R21); or
one of R10, R11 = 1-6C alkoxy, or amino or Het (both optionally substituted by 1-6C alkyl);
R10a, R11a = as R10, R11, but excluding optional substituents CONR10aR11a and NR12R13;
R12, R13 = H or 1-6C alkyl (optionally substituted by V); or
one of R12, R13 = 2-7C alkanoyl or COHet (optionally substituted by 1-6C alkyl); or
R12+R13 = 3-7C alkylene (optionally unsaturated, optionally substituted by 1-6C alkyl, or optionally interrupted by O or NR26);
V = OR6, COOR9, CONR22R23, or NR24R25;
R14, R15 = H or 1-6C alkyl; or
NR14R15 = Het;
R16, R17 = H or 1-6C alkyl (optionally substituted by V); or
one of R16, R17 = aryl or Het (optionally substituted by 1-6C alkyl);
R18, R19 = 1-6C alkyl;
R20, R22-R25 = H or 1-6C alkyl;
R21, R28 = 1-6C alkyl or aryl;
R26 = H, 1-6C alkyl, aryl, COR27, or SO2R28; and
R27 = H, 1-6C alkyl, or aryl.
An INDEPENDENT CLAIM is also included for the preparation of (I).
ACTIVITY - Vasotropic; Tocolytic; Gynecological; Cytostatic; Uropathic; Antianginal; Hypotensive; Cardiant; Antiarteriosclerotic; Cerebroprotective; Antiinflammatory; Antiasthmatic; Ophthalmological; Neuroprotective; Antiallergic; Nootropic; Antipsoriatic.
MECHANISM OF ACTION - Cyclic guanosine monophosphate phosphodiesterase (cGMP PDE) inhibitors.
In tests for cGMP PDE5 inhibition, the most active compounds were ethyl 3-(5-(1-methyl-3-propyl-6,7-dihydro-1H-pyrazolo(4,3-d)pyrimidin-7-on-5-yl)-6-propoxy -3-pyridinyl)propynoate and the methyl ester of the corresponding 3-oxopropanoate, with IC50 values of 0.3 nM.
USE - (I) are of value in both clinical and veterinary medicine for treatment and prophylaxis of both male and female sexual dysfunctions, e.g., erectile, clitoral, hypoactivity, or impotence (claimed) and including those due to spinal cord injury or SSRI drugs. (I) may also be useful in premature labor, dysmenorrhea, benign prostatic hyperplasia (BPH), bladder obstruction or incontinence, angina, hypertension, pulmonary hypertension, obstructive pulmonary disease (COPD), coronary artery disease, congestive heart failure, atherosclerosis, post-PTCA effects, peripheral vascular disease, stroke, nitrate tolerance, bronchitis, asthma, allergic rhinitis, glaucoma, optic neuropathy, macular degeneration, elevated IOP, retinal or arterial occlusion, and irritable

bowel syndrome. Further conditions include pre-eclampsia, Kawasaki syndrome, multiple sclerosis, various neuropathies, Alzheimer's disease, respiratory failure, psoriasis, skin necrosis, cancer and metastases, baldness, esophagitis, anal fissure, hemorrhoids, hypoxia, and stabilization of blood pressure in hemodialysis.
Dwg.0/0

L34 ANSWER 8 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-273753 [28] WPIDS
DOC. NO. CPI: C2001-083059
TITLE: New **pyrimidine**-5-carboxamide compounds are **cGMP**-specific **phosphodiesterase** inhibitors for treating e.g. angina pectoris, allergies and immunodeficiencies.
DERWENT CLASS: B03
INVENTOR(S): DOI, T; MIWA, T; TARUI, N; YAMAMOTO, M
PATENT ASSIGNEE(S): (TAKE) TAKEDA CHEM IND LTD
COUNTRY COUNT: 94
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001027105	A1	20010419	(200128)*	JA	241
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AG AL AM AU AZ BA BB BG BR BY BZ CA CN CR CU CZ DM DZ EE GD GE HR HU ID IL IN IS JP KG KR KZ LC LK LR LT LV MA MD MG MK MN MX NO NZ PL RO RU SG SI SK TJ TM TR TT UA US UZ VN YU ZA					
AU 2000076835	A	20010423	(200147)		
JP 2001233875	A	20010828	(200157)		133
EP 1223170	A1	20020717	(200254)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
JP 2001530323	X	20030507	(200331)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001027105	A1	WO 2000-JP7048	20001011
AU 2000076835	A	AU 2000-76835	20001011
JP 2001233875	A	JP 2000-316833	20001011
EP 1223170	A1	EP 2000-966408	20001011
		WO 2000-JP7048	20001011
JP 2001530323	X	WO 2000-JP7048	20001011
		JP 2001-530323	20001011

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000076835	A	Based on	WO 2001027105
EP 1223170	A1	Based on	WO 2001027105
JP 2001530323	X	Based on	WO 2001027105

PRIORITY APPLN. INFO: JP 1999-289868 19991012

AN 2001-273753 [28] WPIDS
AB WO 200127105 A UPAB: 20010522
NOVELTY - **Pyrimidine**-5-carboxamide compounds (I) are new.
DETAILED DESCRIPTION - **Pyrimidine**-5-carboxamide compounds of formula (I) and their salts are new.
R1 = 3-15 membered heterocyclyl containing 1-5 nitrogen atoms and attached via a nitrogen atom;
X = O, NH (optionally substituted by 1-5C hydrocarbyl), S, SO or SO2;
Y = bond or 1-5C alkylene;
R2 = H, OH, OAlk, SAlk, 3-15C carbocyclyl or Het;
Het = 3-15 membered heterocyclyl containing 1-5 heteroatoms;
Alk = 1-5C alkyl;
one of R3, R4 = H or ZR5; and
the other = ZR5;
Z = bond or optionally substituted 1-10C alkylene;
R5 = H, OH, OAlk, CN, COOAlk, COOH, CONH2, CONHAlk, CON(Alk)2, NH2, NHAlk, N(Alk)2, NHCOOAlk or Het; or
NR3R4 = Het (optionally substituted by 1-8C alkyl, 2-8C alkenyl, 2-8C alkynyl, 7-16C aralkyl, 3-8C cycloalkyl, 3-8C cycloalkenyl, 6-14C aryl, 1-8C alkoxy, 1-3C alkylenedioxy, OH, halo, NH2, NHAlk, N(Alk)2, NHCOOAlk, 1-5C acylamino, 1-5C acyl-1-5C alkylamino, SAlk, CN, NO2, COOAlk, COOH, OCOAlk, oxo, thioxo, 1-6C acyl, SO2NH2, SO2NHAlk or SO2N(Alk)2;
provided that when Y = a bond then R2 = carbocyclyl or Het.
ACTIVITY - Antianginal; Cardiant; Hypotensive; Respiratory-Gen.; Antiarteriosclerotic; Antiallergic; Antiasthmatic; Nephrotropic; CNS-Gen; Immunostimulant; Ophthalmological; Endocrine-Gen.; Vasotropic
MECHANISM OF ACTION - Phosphodiesterase-Inhibitor-V. In a human lung phosphodiesterase V assay 2-(2,3-dihydro-1H-indol-1-yl)-4-((3-fluoro-4-methoxybenzyl)oxy)-N-(3S)-2-oxoazapanyl)-5-pyrimidinecarboxamide had an IC50 value of 0.304 nM.
USE - As **cGMP**-specific **phosphodiesterase** (**cGMP-PDE**) inhibitors, especially **cGMP-PDE**-V inhibitors useful for treating and preventing angina pectoris, cardiac insufficiency, myocardial ischemia, **hypertension**, pulmonary **hypertension**, arteriosclerosis, allergic disorders, asthma, nephropathies, cerebral fibrosis, immunodefficiency, **eye** disorders and male or female sexual dysfunction.
Dwg.0/0

L34 ANSWER 9 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-281958 [29] WPIDS
DOC. NO. CPI: C2001-085891
TITLE: New anhydrous para-toluenesulfonic acid salt of 3-ethyl-5-(5-(4-ethylpiperazin-1-ylsulfonyl)-2-(2-methoxyethoxy)pyridin-3-yl)-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo (4,3-d)pyrimidin-7-one..
DERWENT CLASS: B02
INVENTOR(S): HUGHES, M L; STOREY, R A
PATENT ASSIGNEE(S): (HUGH-I) HUGHES M L; (PFIZ) PFIZER INC; (PFIZ) PFIZER LTD
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

WO 2001027101 A2 20010419 (200129)* EN 26
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000074411 A 20010423 (200147)
US 6350751 B1 20020226 (200220)
BR 2000014656 A 20020611 (200248)
EP 1220855 A2 20020710 (200253) EN
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2003511446 W 20030325 (200330) 27
MX 2002003628 A1 20020801 (200367)
EP 1220855 B1 20040519 (200433) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
DE 60010914 E 20040624 (200442)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001027101	A2	WO 2000-IB1445	20001006
AU 2000074411	A	AU 2000-74411	20001006
US 6350751	B1 Provisional	US 1999-168083P	19991130
		US 2000-657202	20000907
BR 2000014656	A	BR 2000-14656	20001006
		WO 2000-IB1445	20001006
EP 1220855	A2	EP 2000-962772	20001006
		WO 2000-IB1445	20001006
JP 2003511446	W	WO 2000-IB1445	20001006
		JP 2001-530319	20001006
MX 2002003628	A1	WO 2000-IB1445	20001006
		MX 2002-3628	20020410
EP 1220855	B1	EP 2000-962772	20001006
		WO 2000-IB1445	20001006
DE 60010914	E	DE 2000-00010914	20001006
		EP 2000-962772	20001006
		WO 2000-IB1445	20001006

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000074411	A	Based on	WO 2001027101
BR 2000014656	A	Based on	WO 2001027101
EP 1220855	A2	Based on	WO 2001027101
JP 2003511446	W	Based on	WO 2001027101
MX 2002003628	A1	Based on	WO 2001027101
EP 1220855	B1	Based on	WO 2001027101
DE 60010914	E	Based on	EP 1220855
		Based on	WO 2001027101

PRIORITY APPLN. INFO: GB 1999-23968 19991011
AN 2001-281958 [29] WPIDS

Searcher : Shears 571-272-2528

AB WO 200127101 A UPAB: 20010528
NOVELTY - Anhydrous para-toluenesulfonic acid salt of 3-ethyl-5-(5-(4-ethylpiperazin-1-ylsulfonyl)-2-(2-methoxyethoxy)pyridin-3-yl)-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo (4,3-d)pyrimidin-7-one (I) are new.

DETAILED DESCRIPTION - Anhydrous para-toluenesulfonic acid salt of 3-ethyl-5-(5-(4-ethylpiperazin-1-ylsulfonyl)-2-(2-methoxyethoxy)pyridin-3-yl)-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo (4,3-d)pyrimidin-7-one of formula (I) with melting point of 240 plus or minus 5 deg. C is new:

An INDEPENDENT CLAIM is also included for the preparation of the p-toluenesulfonic acid salt of (I).

ACTIVITY - Vasotropic, tocolytic, gynecological, analgesic, cytostatic, uropathic, antianginal, hypotensive, pulmonary, cardiant, antiarteriosclerotic, cerebroprotective, antiasthmatic, antiinflammatory, antiallergic, optical, gastrointestinal, immunomodulator, dermatological, neuroprotective, antidiabetic, nephrotropic, nootropic, antipsoriatic.

MECHANISM OF ACTION - **cGMP PDE5** inhibitors.

USE - (I) are used for the curative or prophylactic treatment of a variety of conditions in humans and animals including: mammalian sexual dysfunction, male erectile dysfunction (MED), impotence, female sexual dysfunction, clitoral dysfunction, female hypoactive sexual desire disorder, female sexual arousal disorder, female sexual pain disorder, female sexual orgasmic dysfunction, sexual dysfunction due to spinal cord injury, selective serotonin re-uptake inhibitor induced sexual dysfunction, premature labor, dysmenorrhea, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, stable, unstable and variant angina, **hypertension**, pulmonary **hypertension**, chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, atherosclerosis, conditions of reduce blood vessel patency, peripheral vascular disease, stroke, nitrate induced tolerance, bronchitis, allergic asthma, chronic asthma, allergic rhinitis, diseases and conditions of the **eye**, diseases characterized by disorders of gut motility, pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, diabetic nephropathy, peripheral diabetic neuropathy, Alzheimer's disease, acute respiratory failure, psoriasis, skin necrosis, cancer, metastasis, baldness, nutcracker esophagus, anal fissure, hemorrhoids and hypoxic vasoconstriction or blood pressure stabilization during hemodialysis.

ADVANTAGE - The p-toluenesulfonic acid salt of (I) has the following advantages: it is crystalline, non-hygroscopic, of suitable melting point, posses chemical stability across a range of temperature and humidity conditions, has acceptable solubility and dissolution profile, acceptable mechanical properties e.g. good compressibility without exhibiting polymorphism, a good drug substance stability profile and can be prepared in good yields e.g. 98.5 % compared to 85 % for the corresponding besylate salt and with ease.

Dwg.0/0

L34 ANSWER 10 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-235120 [24] WPIDS
DOC. NO. NON-CPI: N2001-168089
DOC. NO. CPI: C2001-070483
TITLE: Determining axon viability, useful for identifying axon-protective compounds, potential therapeutic agents for e.g. cerebral ischemia, based on stimulation of soluble guanylate cyclase.
DERWENT CLASS: B04 D16 S03

INVENTOR(S): GARTHWAITE, G; GARTHWAITE, J
PATENT ASSIGNEE(S): (UNLO) UNIV COLLEGE LONDON
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001016359	A2	20010308	(200124)*	EN	28
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000068575	A	20010326	(200137)		
GB 2370636	A	20020703	(200251)		
EP 1220945	A2	20020710	(200253)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001016359	A2	WO 2000-GB3360	20000831
AU 2000068575	A	AU 2000-68575	20000831
GB 2370636	A	WO 2000-GB3360	20000831
		GB 2002-7441	20020328
EP 1220945	A2	EP 2000-956708	20000831
		WO 2000-GB3360	20000831

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000068575	A	Based on	WO 2001016359
GB 2370636	A	Based on	WO 2001016359
EP 1220945	A2	Based on	WO 2001016359

PRIORITY APPLN. INFO: GB 1999-20566 19990831
AN 2001-235120 [24] WPIDS
AB WO 200116359 A UPAB: 20010502
NOVELTY - Determining the viability of an axon by treating it with a substance (I) that stimulates soluble guanylate cyclase (sGC) and if sGC is stimulated then the axon is viable.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(a) identifying substances (II) that protect axons by treating an axon with a test compound and a compound (III) that would normally reduce viability, then determining viability by the new method; and

(b) (III) identified this way.

ACTIVITY - Cytoprotective; Anti-ischemic; Anti-epileptic; Neuroprotective; Antidiabetic; Antiviral; Antimalarial.

USE - The method is used to identify axon-protective compounds (III) that are useful for and in the manufacture of medicaments for the treatment of conditions, in human or veterinary medicine, associated with white matter damage, specifically cerebral or spinal cord ischemia;

epilepsy; multiple sclerosis; **glaucoma**; age-related neuropathy; head/spinal cord trauma; diabetes; viral infection (e.g. by human immune deficiency virus); alcohol abuse; cerebral malaria and motor neurone disease (all claimed).

ADVANTAGE - Axons (but not other white matter cells) respond to **nitric oxide** by greatly increasing production of cyclic guanosine monophosphate, and this response is a sensitive marker of axon viability.

Dwg.0/3

L34 ANSWER 11 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-184342 [19] WPIDS
DOC. NO. CPI: C2001-055401
TITLE: Use of **cyclic guanosine** 3',5'-**monophosphate phosphodiesterase** type 5 inhibitors for treatment of central retinal or posterior ciliary artery occlusion, central retinal vein occlusion, optic neuropathy or macular degeneration.
DERWENT CLASS: B02
INVENTOR(S): LATIES, A M
PATENT ASSIGNEE(S): (PFIZ) PFIZER PROD INC; (LATI-I) LATIES A M
COUNTRY COUNT: 33
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 1074258	A2	20010207	(200119)*	EN	9
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
AU 2000048789	A	20010201	(200119)		
CA 2314571	A1	20010128	(200119)	EN	
JP 2001048788	A	20010220	(200126)		13
HU 2000002963	A2	20010428	(200131)		
KR 2001066966	A	20010711	(200201)		
ZA 2000003768	A	20020327	(200230)		34
US 2002119974	A1	20020829	(200259)		
NZ 518594	A	20030829	(200365)		
AU 768750	B	20040108	(200412)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
EP 1074258	A2		EP 2000-306235	20000721
AU 2000048789	A		AU 2000-48789	20000724
CA 2314571	A1		CA 2000-2314571	20000726
JP 2001048788	A		JP 2000-222162	20000724
HU 2000002963	A2		HU 2000-2963	20000727
KR 2001066966	A		KR 2000-43271	20000727
ZA 2000003768	A		ZA 2000-3768	20000726
US 2002119974	A1	Provisional	US 1999-146095P	19990728
		Cont of	US 2000-607562	20000629
			US 2002-126375	20020419
NZ 518594	A	Div ex	NZ 2000-506009	20000727
			NZ 2000-518594	20000727
AU 768750	B		AU 2000-48789	20000724

Searcher : Shears 571-272-2528

FILING DETAILS:

PATENT NO	KIND	PATENT NO
NZ 518594	A Div ex	NZ 506009
AU 768750	B Previous Publ.	AU 2000048789

PRIORITY APPLN. INFO: US 1999-146095P 19990728; US 2000-607562 20000629; US 2002-126375 20020419

AN 2001-184342 [19] WPIDS

AB EP 1074258 A UPAB: 20010528

NOVELTY - Use of **cyclic guanosine** 3',5'-**monophosphate phosphodiesterase** type 5 inhibitors (I) is claimed for manufacture of a medicament for treating or preventing central retinal or posterior ciliary artery occlusion, central retinal vein occlusion, optic neuropathy or macular (dry) degeneration.

ACTIVITY - Ophthalmological.

A test is described, but no results are given.

MECHANISM OF ACTION - Phosphodiesterase type 5 inhibitor.

USE - Used for manufacture of a medicament for treating or preventing central retinal or posterior ciliary artery occlusion, central retinal vein occlusion, **optic** neuropathy or macular (dry) degeneration. When treating or preventing **optic** neuropathy, the patient group is selected form patients which elevated intraocular pressure, patients greater than 50 years old, patients with family histories of **optic** neuropathy, diabetes or heart disease, patients with **hypertension** or diabetes or patients who have used, or are currently using, corticosteroids that raise intraocular pressure and patients who have undergone intraocular surgery. (I) Are preferably used for treatment of glaucomatous **optic** neuropathy cause or associated with an acute, sub-acute or chronic **glaucoma** comprising chronic (idiopathic) open-angle **glaucoma**, papillary block **glaucoma**, development **glaucoma**, **glaucoma** associated with other **ocular** disorders or especially **glaucomas** associated with elevated episcleral venous pressure, **glaucomas** associated with inflammation and **glaucomas** following intraocular surgery and low tension **glaucoma** or the **optic** neuropathy is anterior ischemic **optic** neuropathy.

ADVANTAGE - Increase in blood flow can be obtained with fewer side effects typically associated with vasodilators such as **nitric oxide** donors e.g. **nitroglycerin**, sodium nitrate, sodium **nitroprusside** and **isosorbide dinitrate**, such as severe hypotension, headache and methemoglobinemia.

Dwg.0/0

L34 ANSWER 12 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-271365 [23] WPIDS

DOC. NO. CPI: C2000-082857

TITLE: New carboline derivatives, useful for treatment of e.g. erectile dysfunction, angina, hypertension, congestive heart failure, stroke, ulcers and dysmenorrhea, are **cGMP** (**cyclic guanosine monophosphate**)-specific **phosphodiesterase** inhibitors.

DERWENT CLASS: B02 C02
INVENTOR(S): BOMBRUN, A; GELLIBERT, F
PATENT ASSIGNEE(S): (ICOS-N) ICOS CORP; (BOMB-I) BOMBRUN A
COUNTRY COUNT: 83
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000015639	A1	20000323	(200023)*	EN	86
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW					
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW					
AU 9910258	A	20000403	(200034)		
BR 9816018	A	20010605	(200138)		
EP 1114048	A1	20010711	(200140)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 2002524564	W	20020806	(200266)		75
US 6462047	B1	20021008	(200269)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000015639	A1	WO 1998-EP6050	19980916
AU 9910258	A	WO 1998-EP6050	19980916
		AU 1999-10258	19980916
BR 9816018	A	BR 1998-16018	19980916
		WO 1998-EP6050	19980916
EP 1114048	A1	EP 1998-952629	19980916
		WO 1998-EP6050	19980916
JP 2002524564	W	WO 1998-EP6050	19980916
		JP 2000-570177	19980916
US 6462047	B1	WO 1998-EP6050	19980916
		US 2001-744859	20010516

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9910258	A	Based on	WO 2000015639
BR 9816018	A	Based on	WO 2000015639
EP 1114048	A1	Based on	WO 2000015639
JP 2002524564	W	Based on	WO 2000015639
US 6462047	B1	Based on	WO 2000015639

PRIORITY APPLN. INFO: WO 1998-EP6050 19980916
AN 2000-271365 [23] WPIDS
AB WO 200015639 A UPAB: 20000516
NOVELTY - Carboline derivatives (I), their salts and solvates, are new.
DETAILED DESCRIPTION - Carboline derivatives of formula (I), their salts and solvates, are new.
A = 5 - 6 membered heteroaryl group containing at least 1 heteroatom selected from O, N and S;

R0 = H or halogen;
R1 = H, nitro, trifluoromethyl, trifluoromethoxy, halogen, cyano, 5 - 6 membered heteroaryl group containing at least 1 heteroatom selected from O, N and S, (optionally substituted by C(O)ORa or 1-4C alkyl), 1-6C alkyl optionally substituted by ORa, 1-3C alkoxy, C(O)Ra, OC(O)Ra, C(O)Ra, (1-4C alkylene)-Het, (1-4C alkylene)-C(O)ORa, O-(1-4C alkylene)-C(O)ORa, (1-4C alkylene)-O-(1-4C alkylene)-C(O)ORa, C(O)NRaSO2Rc, C(O)-(1-4C alkylene)-Het, (1-4C alkylene)-NRaRb, (2-6C alkylene)-NRaRb, C(O)NRaRb, C(O)RaRc, C(O)NRa-(1-4C alkylene)-ORb, C(O)NRa-(1-4C alkylene)-Het, ORa, O-(2-4C alkylene)-NRaRb, O-(1-4C alkylene)-Het, O-(2-4C alkylene)-ORa, O-(2-4C alkylene)-NRaC(O)ORb, NRaRb, NRa-(1-4C alkylene)-NRaRb, NRaC(O)Rb, NRaC(O)NRaRb, N(SO2-(1-4C alkyl))2, NRa(SO2-(1-4C alkyl), SO2NRaRb or OSO2CF3;
R2 = H, halogen, ORa, 1-6C alkyl, nitro or NRaRb; or
R1 + R2 = 3 or 4 membered alkylene or alkenylene chain, optionally containing at least 1 heteroatom component of a 5 or 6 membered ring;
R3 = H, halogen, NO2, trifluoromethoxy, 1-6C alkyl, O-(1-6C alkyl), or C(O)ORa;
R4 = H; or
R3 + R4 = 3 or 4 membered alkylene or alkenylene chain component of a 5 or 6 membered ring, optionally containing at least 1 heteroatom;
Het = 5 or 6 membered heterocyclic group containing at least 1 O, N and/or S, and is optionally substituted by 1-4C alkyl;
Ra, Rb = H or 1-6C alkyl;
Rc = phenyl or 4-6C cycloalkyl, both optionally substituted by 1 or more halogen, C(O)ORa or ORa;
n = 1 - 3; and
m = 1 or 2.

INDEPENDENT CLAIMS are provided for:
(1) a composition comprising (I) and a second active agent for simultaneous, seperate or sequential use; and
(2) a process for the preparation of (I).

ACTIVITY - Vasotropic; centrally active; endocrine; antianginal; hypotensive; respiratory; cytostatic; cardiant; nephrotropic; antiarteriosclerotic; antiaggregant; hemostatic; antiinflammatory; cerebroprotective; antiasthmatic; ophthalmological; antiulcer; gastrointestinal; osteopathic; tocolytic; gynecological; analgesic (all claimed)

MECHANISM OF ACTION - Phosphodiesterase V inhibitor; acetylcholine esterase inhibitor; neutral endopeptidase inhibitor; adrenergic antagonist.

(I) were administered to spontaneously hypertensive rats at 5 mg/kg in 5% DMF and 95% olive oil. Blood pressure was measured using a catheter in the carotid artery and recorded for 5 hours post administration. The area under curve for (E)-1R-1-(1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro- beta -carbolin-2-yl)-3-(pyrrolidin-1-yl)-propen-1-one (Ia) was 9 mm Hg/hour.

USE - As **cGMP (cyclic guanosine monophosphate)**-specific **phosphodiesterase** inhibitors for treatment of erectile dysfunction, angina, hypertension, pulmonary or malignant hypertension, COPD (chronic obstructive pulmonary disease), pheochromocytoma, ARDS (not defined), congestive heart failure, renal failure, atherosclerosis, reduced blood vessel patency, peripheral vascular disease, vascular disorder, thrombocythemia, inflammatory disease, myocardial infarction, stroke, bronchitis, asthma, allergic rhinitis, **glaucoma**, peptic ulcer, gut motility disorder,

post-percutaneous transluminal coronary angioplasty, carotid angioplasty, post-surgical graft stenosis, osteoporosis, pre-term labor, benign prostatic hypertrophy, female sexual dysfunction, dysmenorrhea and IBS (irritable bowel syndrome) (claimed).

ADVANTAGE - Good oral bioavailability, specific for phosphodiesterase 5.

Dwg.0/0

L34 ANSWER 13 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN

ACCESSION NUMBER: 2000-271237 [23] WPIDS

CROSS REFERENCE: 1995-275237 [36]; 1997-132562 [12]; 2001-023419 [03]

DOC. NO. CPI: C2000-082747

TITLE: Composition for simultaneous, separate, or sequential use in the treatment of e.g. erectile dysfunction, comprises a tetracyclic phosphodiesterase inhibitor and a second active agent, e.g. vasodilator, acetylcholine esterase inhibitor.

DERWENT CLASS: B05

INVENTOR(S): DAUGAN, A C; GELLIBERT, F

PATENT ASSIGNEE(S): (ICOS-N) ICOS CORP

COUNTRY COUNT: 87

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000015228	A1	20000323	(200023)*	EN	89
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW					
AU 9957856	A	20000403	(200034)		
BR 9913824	A	20010619	(200140)		
EP 1113800	A1	20010711	(200140)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
JP 2002524516	W	20020806	(200266)		84

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000015228	A1	WO 1999-US19466	19990826
AU 9957856	A	AU 1999-57856	19990826
BR 9913824	A	BR 1999-13824	19990826
		WO 1999-US19466	19990826
EP 1113800	A1	EP 1999-945201	19990826
		WO 1999-US19466	19990826
JP 2002524516	W	WO 1999-US19466	19990826
		JP 2000-569812	19990826

FILING DETAILS:

PATENT NO	KIND	PATENT NO

Searcher : Shears 571-272-2528

AU 9957856	A	Based on	WO 2000015228
BR 9913824	A	Based on	WO 2000015228
EP 1113800	A1	Based on	WO 2000015228
JP 2002524516	W	Based on	WO 2000015228

PRIORITY APPLN. INFO: US 1998-154051 19980916
AN 2000-271237 [23] WPIDS
CR 1995-275237 [36]; 1997-132562 [12]; 2001-023419 [03]
AB WO 200015228 A UPAB: 20021014
NOVELTY - A composition for the simultaneous, separate or sequential use in the treatment of a condition by inhibition of a **cGMP** specific **phosphodiesterase**, comprises a tetracyclic compound (I) and a second therapeutically active agent.

DETAILED DESCRIPTION - A composition for the simultaneous, separate or sequential use in the treatment of a condition by inhibition of a **cGMP** specific **phosphodiesterase**, comprises a tetracyclic compound of formula (I), and salts and solvates, and a second therapeutically active agent.

R0 = H, halogen or 1-6C alkyl;

R1 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, halo-(1-6C)-alkyl, 3-8C cycloalkyl, 3-8C cycloalkyl-(1-3C)-alkyl, aryl-(1-3C)-alkyl or heteroaryl-(1-3C)-alkyl;

R2 = optionally substituted monocyclic aromatic ring selected from benzene, thiophene, furan, pyridine or an optionally substituted bicyclic ring of formula (i), attached to the rest of the molecule via one of the benzene C atoms;

A = 5 - 6 membered ring optionally containing 1 - 2 O, S and or N; and

R3 = H or 1-3C alkyl; or

R1 + R2 = 3-4C alkyl or 3-4C alkenyl.

ACTIVITY - Vasodilator; antianginal; hypotensive; respiratory; antiatherosclerotic; cardiant; vasotropic; hemostatic; antiinflammatory; cerebroprotective; antiasthmatic; antiallergic; ophthalmological; antiulcer; cytostatic; gastrointestinal, CNS active; endocrine.

MECHANISM OF ACTION - Phosphodiesterase inhibitor.

cGMP-PDE (cyclic GMP dependent **phosphodiesterase**) activity was measured using a one-step assay adapted from Wells et al., Biochim. Biophys. Acta, 384, 430 (1975). The reaction medium contained 50 mM Tris-HCl, pH 7.5, 5 mM magnesium acetate, 250 micro g/ml 5'-nucleotidase, 1 mM EGTA (ethylenebis(oxyethylenenitrolo) tetraacetic acid and 0.15 micro M 8-(H3)-**cGMP**. The enzyme used was human recombinant **PDE**-5. (I) were dissolved in DMSO (dimethylsulfoxide) finally present at 2 % in the assay. The incubation time was 30 minutes during which the total substrate conversion did not exceed 30 %. Cis-2,3,6,7,12,12a-hexahydro-6-(2,3-dihydrobenzo(b)-furan-5-yl)-2-methylpyrazine(2',1':6,1)pyrido(3,4-b)indole-1,4-dione (Ia) had an IC50 of less than 10 nM.

USE - The composition is used to treat stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, malignant hypertension, pheochromocytoma, congestive heart failure, acute respiratory distress syndrome, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, postpercutaneous transluminal coronary angioplasty, carotid angioplasty, myocardial infarction, post-bypass surgery graft stenosis, a peripheral vascular disease, a vascular disorder, Raynaud's disease, thrombocythemia, an inflammatory disease, stroke, bronchitis,

chronic asthma, allergic asthma, allergic rhinitis, **glaucoma**, peptic ulcer, osteoporosis, preterm labor, benign prostatic hypertrophy, a gut motility disorder, irritable bowel syndrome or male or female mammalian erectile dysfunction, preferably erectile dysfunction, especially human erectile dysfunction (claimed).
Dwg.0/0

L34 ANSWER 14 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-271232 [23] WPIDS
DOC. NO. CPI: C2000-082742
TITLE: New fused **pyrimidine** derivatives are phosphodiesterase inhibitors, useful for the treatment of e.g. erectile dysfunction, cardiovascular disorders and cancer.
DERWENT CLASS: B02
INVENTOR(S): MACOR, J E; YU, G
PATENT ASSIGNEE(S): (BRIM) BRISTOL-MYERS SQUIBB CO
COUNTRY COUNT: 87
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000015222	A1	20000323	(200023)*	EN	113
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZA ZW					
AU 9961438	A	20000403	(200034)		
EP 1113796	A1	20010711	(200140)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
US 6326379	B1	20011204	(200203)		
AU 751486	B	20020815	(200264)		
JP 2002524512	W	20020806	(200266)		142

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000015222	A1	WO 1999-US21070	19990913
AU 9961438	A	AU 1999-61438	19990913
EP 1113796	A1	EP 1999-948211	19990913
		WO 1999-US21070	19990913
US 6326379	B1 Provisional	US 1998-100665P	19980916
		US 1999-393833	19990910
AU 751486	B	AU 1999-61438	19990913
JP 2002524512	W	WO 1999-US21070	19990913
		JP 2000-569806	19990913

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 9961438	A Based on	WO 2000015222

Searcher : Shears 571-272-2528

EP 1113796	A1	Based on	WO 2000015222
AU 751486	B	Previous Publ.	AU 9961438
		Based on	WO 2000015222
JP 2002524512	W	Based on	WO 2000015222

PRIORITY APPLN. INFO: US 1998-100665P 19980916; US 1999-393833 19990910

AN 2000-271232 [23] WPIDS

AB WO 200015222 A UPAB: 20021105

NOVELTY - Pyrrolo-, pyrazolo- and imidazolo-**pyrimidine** derivatives (I) are new.

DETAILED DESCRIPTION - Pyrrolo-, pyrazolo- and imidazolo-**pyrimidine** derivatives of formula (I) and their salts are new.

E = E1 or E2;

X = X1 or X2;

E1 = OR1, SR1 or NHA1W1;

W1 = heterocyclo, heteroaryl or Cyc;

Cyc = optionally substituted cycloalkyl;

E2 = NHA1W2;

W2 = W3 or CO2alkyl;

R1 = A1W1 or A1W3

W3 = alkoxy, NR15R16 or Ar1;

Ar1 = optionally substituted aryl;

X1 = OA1R2, OR9, NR9R10, N(R5)A2R2 or a group of formula (i)-(iii);

X3 = OR9, OA1OR9, NR9R10, N(R5)A2OR9, N(R5)A1NR9R10 or a group of formula (iv);

A1 = optionally substituted 1-10C alkylene bridge;

one of Y1 and Z = N and the other = N or C(R6);

R3 = H, Cyc, A1Ar1, A1Cyc, or optionally substituted alkyl;

R6 = H, Cyc or A1W4;

W4 = W1 or Ar1;

R4 = H, NR12R13, OR12 or 1- or 3-imidazolyl;

A2 = bond, A1, optionally substituted 2-10C alkenyl or alkynyl bridge having at least one double or triple bond respectively;

R2 = W4, W4A3W4, cyano, OR9, SR9, C(=O)R9, NR9R10, CO2R9, C(=O)NR12R13, SO2NR12R13, NR11C(=O)R19, NR11C(=O)NR12R13, OC(=O)NR12R13 (provided that A2 is not a bond), NR11CO2R19, C(=O)N(R11)CH2CO2R19, N (when A2 is alkynyl ending in a triple bond) or NH (when A2 is an alkenyl ending in a double bond);

R25 = W4, W4A3W4, cyano, OR9, SR9, C(=O)R11, CO2R19, C(=O)NR12R13, SO2NR12R13, NR9C(=O)R10, NR11C(=O)NR12R13, OC(=O)NR12R13 (provided that A2 is not a bond), NR11CO2R19, C(=O)N(R11)CH2CO2R19, N (when A2 is alkynyl ending in a triple bond) or NH (when A2 is an alkenyl ending in a double bond);

A3 = A2, (CH2)dO(CH2)e, (CH2)dS(CH2)e or (CH2)dC(=O)(CH2)e;

d, e = 0-6;

R5 = H, optionally substituted alkyl, W4, A1Ar1, A1-heterocyclo or A1-heteroaryl;

R9, R10-R13, R15, R16, R19 = H, optionally substituted alkyl, W4 or A1W4; or

NR12R13 = heterocyclic ring;

het = 4-8 membered monocyclic heterocyclo or heteroaryl ring containing up to 3 additional heteroatoms (up to 2 additional heteroatoms when the ring is 4 membered) selected from 1 or 2 O and/or 1 or 2 S and/or 1-3 N;

ring B1 = W4 having 2C in common with het;

ring B2 = W4 having 1C in common with het;
R21 = H, alkyl, halogen, OH, trifluoromethyl, amino, alkoxy or carboxy;
R22 = keto, C(=O)R23, CO2R23, NHC(=O)R23, N(alkyl)2, A1T1 or A2W4;
T1 = T2 or alkoxy;
T2 = OH, NR9R10 or carboxy;
n = 1 or 2;
m = 0 or 1; and
R23 = alkyl, NR9R10, A1T2 or A2W4;
provided that:
(1) when E = E1, X = X1; and
(2) when E = E2, X = X2.
NB X3 is defined but is not used in the main claim.
An INDEPENDENT CLAIM is also included for a composition comprising (I; X = X3; E = E2) or its salt for the treatment of cyclic guanosine 3'.5'-monophosphate (cGMP) associated conditions.
ACTIVITY - Vasotropic; CNS; endocrine; hypotensive; antianginal; cardiant; antiarteriosclerotic; antilipemic; thrombolytic; cardiovascular; cerebroprotective; respiratory; antiinflammatory; antiasthmatic; antiallergic.
No relevant biological data is given.
MECHANISM OF ACTION - Phosphodiesterase IV inhibitor.
USE - (I) are useful for the treatment of erectile dysfunction (claimed), hypertension, angina, heart failure, restenosis, atherosclerosis, dyslipidemia, reduced blood vessel patency, thrombus, myocardial infarction, peripheral vascular disease, stroke, bronchitis, asthma, allergic rhinitis, glaucoma, gut motility disorders and cancer.
Dwg.0/0

L34 ANSWER 15 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-006442 [01] WPIDS
CROSS REFERENCE: 1996-476736 [47]
DOC. NO. CPI: C2001-001413
TITLE: Use of a combination of a tetracyclic derivative, which inhibits **cGMP**-specific **PDE**, and second active agent for treatment of e.g. erectile dysfunction and cardiovascular disorders.
DERWENT CLASS: B02
INVENTOR(S): DAUGAN, A C; LABAUDINIERE, R F
PATENT ASSIGNEE(S): (ICOS-N) ICOS CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6143757	A	20001107	(200101)*		18

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6143757	A CIP of	WO 1996-EP3023	19960711
		US 1998-154619	19980916

PRIORITY APPLN. INFO: US 1998-154619 19980916; WO

1996-EP3023 19960711

AN 2001-006442 [01] WPIDS
CR 1996-476736 [47]
AB US 6143757 A UPAB: 20001230
NOVELTY - A combination of a tetracyclic derivative (I) and second active agent can be used to treat conditions where inhibition of a **cyclic guanosine** 3',5'-**monophosphate** specific **phosphodiesterase** (**cGMP**-specific **PDE**) is of benefit.

DETAILED DESCRIPTION - Use of a combination of a tetracyclic derivative of formula (I) and second active agent, for simultaneous, separate or sequential administration in the treatment of a condition where inhibition of a **cGMP**-specific **PDE** is of benefit, is new.

R0 = H, halo or 1-6C alkyl;

R1 = H, 1-6C alkyl (optionally substituted by 1 or more Q), 3-6C cycloalkyl, phenyl or 5- or 6-membered heterocyclic ring (containing at least one O, N or S, optionally substituted by 1 or more 1-6C alkyl, and optionally linked to the N to which R1 is attached via 1-6C alkyl);

Q = phenyl, halo, CO2Ra or -NRaRb;

R2 = 3-6C cycloalkyl, phenyl (optionally substituted by 1 or more Q') 5- or 6-membered heterocyclic ring (containing at least one O, N or S) or a bicyclic ring of formula (i);

A = 5- or 6-membered heterocyclic ring containing at least one O, N or S;

Q' = -ORa, -NRaRb, halo, OH, CF3, CN or NO2;

Ra, Rb = H or 1-6C alkyl.

ACTIVITY - Vasotropic; antianginal; hypotensive; cardiant; nephrotropic; antiarteriosclerotic; thrombolytic; antiinflammatory; cerebroprotective; antiasthmatic; antiallergic; ophthalmological; antiulcer; osteopathic. Conscious spontaneously hypertensive rats were administered (5R,11aR)-2-benzyl-5-(3,4-methylenedioxyphenyl)-5,6,11,11a-tetrahydro-1H-imidazo(1',5':1,6)pyrido(3,4-b)indole-1,3-(2H)-dione (32) (10 mg/kg i.v.) Blood pressure was measured from a catheter inserted in the carotid artery and recorded for 5 hours after administration. Results gave 60 mmHg.hour AUC (area under the curve of the fall in blood pressure over the time).

MECHANISM OF ACTION - **Cyclic guanosine** 3',5'-**monophosphate** specific **phosphodiesterase** (**cGMP**-specific **PDE**) inhibitors.

USE - For treating erectile dysfunction, angina (stable, unstable or variant), hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, malignant hypertension, pheochromocytoma, congestive heart failure, acute renal failure, atherosclerosis, a condition of reduced blood vessel potency, a peripheral vascular disease, a vascular disorder, thrombocythemia, an inflammatory disease, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, **glaucoma**, peptic ulcer, a gut motility disorder, postpercutaneous transluminal coronary angioplasty, carotid angioplasty, post-bypass surgery graft stenosis, osteoporosis, preterm labor, benign prostatic hypertrophy, or irritable bowel syndrome.

Dwg.0/0

L34 ANSWER 16 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2001-023419 [03] WPIDS

CROSS REFERENCE: 1995-275237 [36]; 1997-132562 [12]; 2000-271237 [23]
DOC. NO. CPI: C2001-007100
TITLE: Use of hexahydro-pyrazino-pyrido-indole-dione derivative and another drug for treatment of conditions benefiting from **cGMP**-specific **phosphodiesterase** inhibition e.g. erectile dysfunction.
DERWENT CLASS: B05 C03
INVENTOR(S): DAUGAN, A C; GELLIBERT, F
PATENT ASSIGNEE(S): (ICOS-N) ICOS CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6143746	A	20001107	(200103)*		30

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6143746	A CIP of	WO 1995-EP183	19950119
		US 1998-154051	19980916

PRIORITY APPLN. INFO: GB 1995-14474 19950714; GB 1994-1090 19940121; GB 1995-14465 19950714
AN 2001-023419 [03] WPIDS
CR 1995-275237 [36]; 1997-132562 [12]; 2000-271237 [23]
AB US 6143746 A UPAB: 20010116
NOVELTY - A combination of a 2,3,6,7,12,12a-hexahydro-pyrazino(2',1';6,1)pyrido(3,4-b)indole-1,4-dione derivative (I) and another drug (II) is claimed for simultaneous, separate or sequential use in the treatment of conditions where inhibition of **cGMP**-specific **phosphodiesterase** (**PDE**) is of therapeutic benefit.

DETAILED DESCRIPTION - A combination of a 2,3,6,7,12,12a-hexahydro-pyrazino(2',1';6,1)pyrido(3,4-b)indole-1,4-dione of formula (I) and another drug (II) is claimed for simultaneous, separate or sequential use in the treatment of conditions where inhibition of **cGMP**-specific **phosphodiesterase** (**PDE**) is of therapeutic benefit.

R0 = H, halogen or 1-4C alkyl;

R1 = H, 1-6C alkyl, 2-6C alkenyl, 2-6C alkynyl, 1-6C haloalkyl, 3-8C cycloalkyl, (3-8C)cycloalkyl(1-3C)alkyl, aryl(1-3C)alkyl or heteroaryl(1-3C)alkyl;

R2 = phenyl, thienyl, furyl or pyridyl, where phenyl is optionally fused to a 5- or 6-membered ring containing 0-2 heteroatoms selected from O, S and N; and

R3 = H or 1-3C alkyl; or

R1+R3 = 3-4C alkylene or alkenylene.

ACTIVITY - Vasotropic; antianginal; hypotensive; cardiant; nephrotropic; antiarteriosclerotic; vasotropic; antiinflammatory; cerebroprotective; antiasthmatic; antiallergic; opthalmalogical; antiulcer; osteopathic; laxative; antidiarrheic.

MECHANISM OF ACTION - Phosphodiesterase-5 inhibitor.

The hypotensive effects of (I) and (II) were studied in conscious spontaneously hypertensive rats. Various mixtures of (I) and (II) gave

results expressed as Area Under Curve (AUC) from 0-5 hours in mmHg.hours, of the fall in blood pressure over time of 77-171.

USE - The combination is especially useful for treating conditions where inhibition of PDE5 is of therapeutic benefit, in humans or nonhuman animals, especially erectile dysfunction, stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, acute respiratory distress syndrome, malignant hypertension, pheochromocytoma, congestive heart failure, acute renal failure, chronic renal failure, atherosclerosis, a condition of reduced blood vessel patency, peripheral vascular disease, a vascular disorder, thrombocythemia, inflammatory disease, myocardial infarction, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, **glaucoma**, peptic ulcer, gut motility disorders, post-percutaneous transluminal coronary or carotid angioplasty, post-bypass surgery graft stenosis, osteoporosis, preterm labor, benign prostatic hypertrophy or irritable bowel syndrome.

Dwg.0/0

L34 ANSWER 17 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 2000-282560 [24] WPIDS
CROSS REFERENCE: 1998-076777 [07]
DOC. NO. CPI: C2000-085192
TITLE: Combinations comprising carboline derivatives and second therapeutic agent for simultaneous, separate or sequential treatment of conditions where inhibition of **cGMP**-specific **PDE** is of therapeutic benefit.
DERWENT CLASS: B02
INVENTOR(S): BOMBRUN, A
PATENT ASSIGNEE(S): (ICOS-N) ICOS CORP
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6043252	A	20000328	(200024)*		40

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6043252	A	CIP of	WO 1997-EP2277	19970505
			US 1998-154052	19980916

PRIORITY APPLN. INFO: US 1998-154052 19980916; WO 1997-EP2277 19970505

AN 2000-282560 [24] WPIDS
CR 1998-076777 [07]
AB US 6043252 A UPAB: 20000522
NOVELTY - Combinations comprising:

(a) carboline derivatives and their salts and solvates; and

(b) second therapeutically active agent, for simultaneous, separate or sequential use in the treatment of conditions where inhibition of a cyclic-guanylic acid (**cGMP**)-specific **phosphodiesterase** (**PDE**) is of therapeutic benefit.

DETAILED DESCRIPTION - Carboline derivatives in the combination are of formula (I):
R0 = H or halo;
R1 = H, nitro, trifluoromethyl, trifluoromethoxy, halo, cyano, 5-6-membered heterocyclic group containing at least one heteroatom chosen from O, S and N optionally substituted by C(=O)ORa or 1-4C alkyl, 1-6C alkyl optionally substituted by ORa, 1-3C alkoxy, C(=O)Ra, OC(=O)Ra, C(=O)ORa, 1-4C alkylene-C(=O)ORa, O-(1-4C) alkylene-C(=O)ORa, 1-4C alkylene-O-(1-4C) alkylene-C(=O)ORa, C(=O)NRaSO2Rc, C(=O)-(1-4C) alkylene-Het, 1-4C alkylene-NRaRb, 2-6C alkenylene-NRaRb, C(=O)NRaRb, C(=O)NRaRc, C(=O)NRa-(1-4C) alkylene-ORb, C(=O)NRa-(1-4C) alkylene-Het, ORa O-(2-4C) alkylene-NRaRb, O-(1-4C) alkylene-CH(ORa) CH2NRaRb, O-(1-4C) alkylene-Het, O-(2-4C) alkylene-ORa, O-(2-4C) alkylene-NRa-C(=O)ORb, NRaRb, NRa-(1-4C) alkylene-NRaRb, NRaC(=O)Rb, NRaC(=O)NRaRb, N-(SO2-(1-4C) alkyl)2, NRa(SO2-1(1-4C) alkyl), SO2NRaRb or OSO2-trifluoromethyl;
R2 = H, halo, ORa, 1-6C alkyl, NO2, NRaRb; or
R1+R2 = 3-4-membered alkylene or alkenylene chain component of a 5-6-membered ring optionally containing at least one heteroatom chosen from O, S or N;
R3 = H, halo, nitro, trifluoromethoxy, 1-6C alkyl or C(=O)ORa;
R4 = H; or
R3+R4 = 3-4-membered alkylene or alkenylene chain component of a 5-6-membered ring optionally containing at least one heteroatom;
Het = 5-6-membered heterocyclic ring containing at least one heteroatom chosen from O, S or N and optionally substituted by 1-4C alkyl;
Ra, Rb = H or 1-6C alkyl;
Rc = phenyl or 4-6C cycloalkyl optionally substituted by one or more of halo, one or more of C(=O)ORa or one or more of ORa;
n = 1-3; and
m = 1-2.

ACTIVITY - Antianginal, Hypotensive; Cardiant; Antiarteriosclerotic; Antiinflammatory; Cerebroprotective; Antiasthmatic; Antiallergic; Antiulcer; Osteopathic; Cytostatic; Vasotropic.

The hypotensive effects of 17 test compounds (I) were examined in conscious spontaneously hypertensive rats (SHR). The compounds were administered at doses of 5 mg/kg in a mixture of 5% dimethylformamide and 95% olive oil. Blood pressure was measured from a catheter inserted in the carotid artery and recorded for 5 hours after administration. The results were expressed as area-under-the-curve (AUC 0-5) (mmHg/hour) of the fall in blood pressure over time. The results ranged from 52-128 mmHg/hour.

MECHANISM OF ACTION - **cGMP**-specific **PDE** inhibitor; vasodilator; alpha -adrenergic blocker; mixed alpha , beta -blocker; alpha 2-adrenergic blocker; ACE inhibitor; NEP inhibitor; centrally acting dopaminergic agent; calcium channel blocker; diuretic.

Test compounds (I) were tested for **cGMP-PDE** activity using a one-step assay Wells et al. Biochim Biophys Acta 1975; 384: 430 and human recombinant **PDE5**. The test compounds were dissolved in dimethylsulfoxide finally present at 2% in the assay. The incubation period was 30 minutes, during which the total substrate conversion did not exceed 30%. The IC50 values were determined and ranged from 2-72 nM.

USE - The combinations are used for simultaneous, separate or sequential treatment of conditions where inhibition of **cGMP** -specific **PDE** is of therapeutic benefit including stable angina, unstable angina, variant angina, hypertension, pulmonary hypertension, chronic obstructive pulmonary disease, malignant hypertension,

pheochromocytoma, congestive heart failure, acute respiratory distress syndrome, acute renal failure, chronic renal failure, atherosclerosis, conditions of reduced blood vessel patency, post-percutaneous transluminal coronary angioplasty, carotid angioplasty, myocardial infarction, post-bypass surgery graft stenosis, peripheral vascular disease, vascular disorders, Raynaud's disease, thrombocythemia, inflammatory disease, stroke, bronchitis, chronic asthma, allergic asthma, allergic rhinitis, **glaucoma**, peptic ulcer, osteoporosis, pre-teem labor, benign prostatic hypertrophy, gut motility disorder or irritable bowel syndrome, or erectile dysfunction in male or female animals (claimed). Dwg.0/0

L34 ANSWER 18 OF 19 EMBASE on STN

ACCESSION NUMBER: 1999224434 EMBASE

TITLE: Multiple cyclic nucleotide phosphodiesterases in human trabecular meshwork cells.

AUTHOR: Zhou L.; Thompson W.J.; Potter D.E.

CORPORATE SOURCE: L. Zhou, Dept. of Pharmacology/Toxicology, Morehouse School of Medicine, 720 Westview Drive SW, Atlanta, GA 30310, United States

SOURCE: Investigative Ophthalmology and Visual Science, (1999) 40/8 (1745-1752).
Refs: 38
ISSN: 0146-0404 CODEN: IOVSDA

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 002 Physiology
012 Ophthalmology
029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Purpose. To characterize cyclic nucleotide **phosphodiesterase** isozyme activities in human trabecular meshwork cells and primary cultures of porcine trabecular meshwork cells. Methods. Radioimmunoassay of acetylated acid extracts was used to determine changes in cyclic adenosine monophosphate (cAMP) and cyclic quanosine monophosphate (**cGMP**) in human trabecular meshwork cells treated with **phosphodiesterase** isoform selective inhibitors. Cyclic nucleotide **phosphodiesterase** activities were measured using the two-step radioisotope procedure (Thompson). Enzyme activities in the supernatant of human cells were fractionated using anion-exchange chromatography. Additionally, human and porcine trabecular meshwork cell transcripts of **phosphodiesterase** family-specific isoforms were studied by reverse transcription-polymerase chain reaction and nucleotide sequencing. Results. In intact human cells, selective inhibitors for **phosphodiesterase** 4 (rolipram) and 5 (E4021) gene families were effective in augmenting cyclic nucleotide accumulation in response to isoproterenol or sodium **nitroprusside**, respectively, cAMP and **cGMP** hydrolytic activities, resolved using Trisacryl M anion-exchange chromatography, showed a cAMP **phosphodiesterase** peak that was minimally sensitivity to **cGMP** but modestly inhibited by rolipram and a **cGMP** **phosphodiesterase** peak that was sensitive to inhibition by E4021. Further evaluation of the **cGMP** **phosphodiesterase** demonstrated Michaelis-Menten kinetics and competitive inhibition by E4021. Messenger RNA transcripts for **phosphodiesterase** 4, 5, and

7 isozymes were isolated in human trabeCular meshwork cells. However, in porcine trabecular meshwork cells only isozymes for **phosphodiesterase** 4 and 5 isozymes were detected. Conclusions. Human trabecular meshwork cells express **phosphodiesterase** 4, 5, and 7 gene family isoforms and enzyme activities, suggesting that selective isoform inhibitors could be used to augment the actions of antiglaucoma drugs that use cyclic nucleotides as second messengers.

L34 ANSWER 19 OF 19 WPIDS COPYRIGHT 2004 THE THOMSON CORP on STN
ACCESSION NUMBER: 1992-009337 [02] WPIDS
DOC. NO. CPI: C1992-004005
TITLE: New 5-phenyl-1,6-di hydro-7H-pyrazolo-(4,6-d)-pyrimidin-7-one derivs. - **cyclic guanosine** 3',5'-**mono phosphate** **phosphodiesterase** inhibitors, for treating angina hypertension gastrointestinal disorders, etc..
DERWENT CLASS: B02
INVENTOR(S): BELL, A S; BROWN, D; TERRETT, N K; BELL, E S
PATENT ASSIGNEE(S): (PFIZ) PFIZER INC; (PFIZ) PFIZER LTD; (PFIZ) PFIZER CORP; (PFIZ) PFIZER & CO INC
COUNTRY COUNT: 33
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 463756	A	19920102	(199202)*		26
R: AT BE CH DE ES FR GB GR IT LI LU NL SE					
BR 9102560	A	19920121	(199208)		
NO 9102366	A	19911223	(199208)		
CA 2044748	A	19911221	(199211)		
FI 9103017	A	19911221	(199213)		
PT 98011	A	19920331	(199216)		
AU 9179155	A	19920319	(199221)		
CN 1057464	A	19920101	(199237)		
CS 9101876	A2	19920415	(199243)		
HU 61312	T	19921230	(199306)		
ZA 9104707	A	19930224	(199315)		46
NZ 238586	A	19930826	(199337)		
US 5250534	A	19931005	(199341)		12
JP 06041133	A	19940215	(199411)		20
TW 222633	A	19940421	(199422)		
US 5346901	A	19940913	(199436)		11
EP 463756	B1	19950419	(199520)	EN	37
R: AT BE CH DE DK ES FR GB GR IT LI LU NL SE					
CZ 279289	B6	19950412	(199523)		
DE 69108991	E	19950524	(199526)		
ES 2071919	T3	19950701	(199533)		
FI 95132	B	19950915	(199542)		
NO 178029	B	19951002	(199545)		
JP 07121945	B2	19951225	(199605)		19
IE 66040	B	19951213	(199608)		
IL 98482	A	19951127	(199608)		
KR 9406628	B1	19940723	(199619)		
RU 2047617	C1	19951110	(199628)		16
BR 1100028	A3	19970422	(199723)		
US 5719283	A	19980217	(199814)		10

CA 2044748	C	19980203 (199816)
RU 2114114	C1	19980627 (199954)
HU 218945	B	20010131 (200112)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
EP 463756	A		EP 1991-305137	19910607
AU 9179155	A		AU 1991-79155	19910619
CN 1057464	A		CN 1991-104162	19910619
CS 9101876	A2		CS 1991-1876	19910619
HU 61312	T		HU 1991-2061	19910620
ZA 9104707	A		ZA 1991-4707	19910619
NZ 238586	A		NZ 1991-238586	19910618
US 5250534	A	Cont of	US 1991-717227	19910618
			US 1992-882988	19920514
JP 06041133	A		JP 1991-147304	19910619
TW 222633	A		TW 1991-104709	19910618
US 5346901	A	Cont of	US 1991-717227	19910614
		Div ex	US 1992-882988	19920514
			US 1993-84827	19930629
EP 463756	B1		EP 1991-305137	19910607
CZ 279289	B6		CS 1991-1876	19910619
DE 69108991	E		DE 1991-608991	19910607
			EP 1991-305137	19910607
ES 2071919	T3		EP 1991-305137	19910607
FI 95132	B		FI 1991-3017	19910619
NO 178029	B		NO 1991-2366	19910618
JP 07121945	B2		JP 1991-147304	19910619
IE 66040	B		IE 1991-2094	19910619
IL 98482	A		IL 1991-98482	19910613
KR 9406628	B1		KR 1991-10160	19910619
RU 2047617	C1		SU 1991-4895624	19910619
BR 1100028	A3		BR 1996-1100028	19960809
US 5719283	A	Cont of	US 1991-717227	19910618
		Div ex	US 1992-882988	19920514
		Div ex	US 1993-84827	19930629
			US 1994-265295	19940624
CA 2044748	C		CA 1991-2044748	19910617
RU 2114114	C1		SU 1991-5052507	19910619
HU 218945	B		HU 1991-2061	19910620

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 5346901	A	Div ex	US 5250534
CZ 279289	B6	Previous Publ.	CS 9101876
DE 69108991	E	Based on	EP 463756
ES 2071919	T3	Based on	EP 463756
FI 95132	B	Previous Publ.	FI 9103017
NO 178029	B	Previous Publ.	NO 9102366
JP 07121945	B2	Based on	JP 06041133
US 5719283	A	Div ex	US 5250534
		Div ex	US 5346901

Searcher : Shears 571-272-2528

HU 218945 B Previous Publ. HU 61312

PRIORITY APPLN. INFO: GB 1990-13750 19900620
AN 1992-009337 [02] WPIDS
AB EP 463756 A UPAB: 19931006
Dihydro-pyrazolo(4,3-d) pyrimidinone derivs. of formula (I) and their pharmaceutically acceptable salts are new. R1= H, 1-3C alkyl, 3-5C cycloalkyl or 1-3C perfluoroalkyl; R2= H; 1-6C alkyl opt. substd. by OH, 1-3C alkoxy or 3-6C cycloalkyl; or 1-3C perfluoroalkyl; R3= 1-6C alkyl, 3-6C alkenyl, 3-6C alkynyl, 3-7C cycloalkyl, 1-6C perfluoroalkyl or 3-6C cycloalkyl-(1-6C); alkyl; Q= pyrrolidino, piperidino, morpholino or 4-R6-piperazino all substd. by R5; R5= H, 1-4C alkyl, 1-3C alkoxy, NR7R8 or CONR7R8; R6= H, 1-6C alkyl; 2-6C alkyl substd. by 1-3C alkoxy, OH, NR7R8 or CONR7R8; CONR7R8; CSNR7R8; or C(=NH)NR7R8; R7 and R8= H, 1-4C alkyl, 1-3C alkoxy-(2-4C)alkyl or 2-4C hydroxyalkyl.
USE - Selective inhibitors of **cyclic guanosine 3',5'-monophosphate phosphodiesterase** (**cGMP PDE**). Elevates **cGMP** levels which can produce pref. platelet anti-aggregatory, anti-vasospastic and vasodilating activity and potentiation of the effects of endothelium derived relaxing factor (EDRF) and nitrovasodilators. Useful for treating cardiovascular disorders e.g. angina, hypertension, congestive heart failure, atherosclerosis conditions of reduced blood vessel potency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease and stroke, bronchitis, chronic or allergic-asthma, allergic rhinitis, **glaucoma** and disorders associated with gut motility (e.g. irritable bowel syndrome). 0/0
ABEQ ZA 9104707 A UPAB: 19931006
Pyrazolopyrimidinone antianginal agents. New pyrazolo-pyrimidinone cpds. of formula (I) and then pharmaceutically acceptable salts are claimed. R1 is H, 1-3C alkyl, 3-5C cycloalkyl or 1-3C perfluoro-alkyl; R2 is H, 1-6C alkyl substd. by OH 1-5C alkoxy, or C3-6C cycloalkyl, or 1-5 perfluoroalkyl; R3 is 1-6C alkyl, 3-6C alkenyl, 3-6C alkynyl, 3-7C cycloalkyl, 1-6C perfluoroalkyl or (3-6C cycloalkyl) 1-6C alkyl; R4 taken together with the N atom to which it is attached completes a pyrrolidinyl, piperidino, morpholino, or 4-N-(R6)-piperazinyl group; R6 is H, 1-6C alkyl, 1-3C alkoxy, NR7R8, or CONR7R8 R6 is H, 1-6C alkyl, C1 1-3C alkoxy) 2-6C alkyl, OH, 2-6C alkyl, (R7R8N) 2-6C alkyl, (R7R8NCO)1-6C alkyl, CONR7R8, CSNR7R8 CSNR7R8 or C(NH)NR7R8, R7 and R8 are each independently H, 1-4C alkyl, (1-3C alkoxy) 2-4C alkyl or hydroxy 2-4C alkyl.
USE/ADVANTAGE - (I) are selective **cGMP PDE** inhibitors useful in the treatment of cardiovascular disorders such as angina, hypertension, heart failure and atherosclerosis.
ABEQ US 5250534 A UPAB: 19931130
Pyrazolo(4,3-d)-pyrimidin-7-ones of formula (I) and salts are new. In the formula , R1 is H, 1-3C alkyl, 3-5C cycloalkyl, or 1-3C pefluoroalkyl; R2 is H, 1-6C alkyl opt. substd. by OH, 1-3C alkoxy or 3-6C cycloalkyl, or 1-3C perfluoroalkyl; R3 is 1-6C alkyl, 3-6C-alkenyl or -alkynyl, 3-7C cycloalkyl, 1-6C perfluoroalkyl or (3-6C cycloalkyl) 1-6C alkyl; R4 together with attached N compeltes 4- N-(R6)-piperazinyl gp.; R5 is H, 1-4C alkyl, 1-3C alkoxy, NR7R8 or CONR7R8; R6 is H, 1-6C alkyl, (1-3C)alkoxy 2-6C alkyl, OH (2-6C) alkyl, (R7R8N) 2-6C alkyl, (R7R8NCO) 1-6C alkyl, CONR7R8, CSNR7R8, or C(NH)NR7R8; R7 and R8 are independently H, 1-4C alkyl, (1-3C alkoxy) 2-4C alkyl, or OH(2-4C) alkyl.
Specifically claimed cpds. include 5-(2-allylkoxy -5-(4-methylpiperazinyl sulphonyl)phenyl) -1-methyl-3-n-propyl

-1,6-dihydroxy -7H-pyrazolo(4,3-d) -pyrimidin-7-one.
USE - (I) inhibit **cGMP PDE** selectively (but not cAMP **PDE**) and are used to treat angina, hypertension, heart failure and atherosclerosis. Adult dosage is e.g, 4-800 (2-400) mg/day.
Dwg.0/0

ABEQ US 5346901 A UPAB: 19941102
Pyrazolopyrimidinone cpds. of formula (I) and salts are new. In the formula, R1 is H, 1-3C alkyl, 3-5C cycloalkyl or 1-3C perfluoroalkyl; R2 is H, 1-6C alkyl, opt. substd. by OH, 1-3C alkoxy, 3-6C cycloalkyl or 1-3C perfluoroalkyl; R3 is 1-6C alkyl, 3-6C-alkenyl or -alkynyl, 3-7C cycloalkyl, 1-6C perfluoroalkyl or (3-6C cycloalkyl)1-6C alkyl; R4 with attached N forms pyrrolidinyl, piperidino or morpholino; R5 is H, 1-4C alkyl, 1-3C alkoxy, NR7R8 or CONR7R8; R7 and R8 are H, 1-4C alkyl, (1-3C alkoxy) 2-4C alkyl or OH(2-4C)alkyl.
USE - (I) are selective c-GMP PDE inhibitors w.r.t. c-AMP raising c-GMP levels. Compsns. are used to treat angina, hypertension, heart failure and atherosclerosis. Dosage is e.g. 4-800 mg for adult orally or 1-400 mg intravenously, bucally or sublingually.
Dwg.0/0

ABEQ EP 463756 B UPAB: 19950530
A compound of the formula (I) wherein R1 is H, C1-C3 alkyl, C3-C5 cycloalkyl or C1-C3 perfluoroalkyl; R2 is H, C1-C6 alkyl optionally substituted by OH, C1-C3 alkoxy or C3-C6 cycloalkyl, or C1-C3 perfluoroalkyl; R3 is C1-C6 alkyl, C3-C6 alkenyl, C3-C6 alkynyl, C3-C7 cycloalkyl, C1-C6 perfluoroalkyl or (C3-C6 cycloalkyl)C1-C6 alkyl; R4 taken together with the nitrogen atom to which it is attached completes a pyrrolidinyl, piperidino, morpholino, or 4-N-(R6)-piperazinyl group; R5 is H, C1-C4 alkyl, C1-C3 alkoxy, NR7R8 or CONR7R8; R6 is H, C1-C6 alkyl, (C1-C3 alkoxy) C2-C6 alkyl, hydroxy C2-C6 alkyl, (R7R8N)C2-C6 alkyl, (R7R8NCO)C1-C6 alkyl, CONR7R8, CSNR7R8 or C(NH)NR7R8; R7 and R8 are each independently H, C1-C4 alkyl, (C1-C3 alkoxy)C2-C4 alkyl or hydroxy C2-C4 alkyl; and pharmaceutically acceptable salts thereof.
Dwg.0/0

ABEQ US 5719283 A UPAB: 19980406
Dihydro-pyrazolo(4,3-d) pyrimidinone derivs. of formula (I) and their pharmaceutically acceptable salts are new. R1= H, 1-3C alkyl, 3-5C cycloalkyl or 1-3C perfluoroalkyl; R2= H; 1-6C alkyl opt. substd. by OH, 1-3C alkoxy or 3-6C cycloalkyl; or 1-3C perfluoroalkyl; R3= 1-6C alkyl, 3-6C alkenyl, 3-6C alkynyl, 3-7C cycloalkyl, 1-6C perfluoroalkyl or 3-6C cycloalkyl-(1-6C); alkyl; Q= pyrrolidino, piperidino, morpholino or 4-R6-piperazino all substd. by R5; R5= H, 1-4C alkyl, 1-3C alkoxy, NR7R8 or CONR7R8; R6= H, 1-6C alkyl; 2-6C alkyl substd. by 1-3C alkoxy, OH, NR7R8 or CONR7R8; CONR7R8; CSNR7R8; or C(=NH)NR7R8; R7 and R8= H, 1-4C alkyl, 1-3C alkoxy-(2-4C)alkyl or 2-4C hydroxyalkyl.
USE - Selective inhibitors of **cyclic guanosine 3',5'-monophosphate phosphodiesterase (cGMP PDE)**. Elevates **cGMP** levels which can produce pref. platelet anti-aggregatory, anti-vasospastic and vasodilating activity and potentiation of the effects of endothelium derived relaxing factor (EDRF) and nitrovasodilators. Useful for treating cardiovascular disorders e.g. angina, hypertension, congestive heart failure, atherosclerosis conditions of reduced blood vessel potency (e.g. post-percutaneous transluminal coronary angioplasty), peripheral vascular disease and stroke, bronchitis, chronic or allergic-asthma, allergic rhinitis, **glaucoma** and disorders associated with gut motility (e.g. irritable bowel syndrome).

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